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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1931

ORIGINAL ARTICLES.

EXPERIMENTAL CANCER RESEARCH.*

By William H. Woglom, M.D.,

NEW YORK.

(From the Institute of Cancer Research, Columbia University, F. C. Wood, Director.)

When a colleague shows signs of pessimism about the progress of cancer research it is my custom to ask whether he would rather have had malignant disease thirty years ago or have it today. The answer has always been in favor of the present, showing that even those who in their darker moments despair of ultimate solution of the cancer problem realize that some progress has been made.

Reflect for a moment, if you please, on the magnitude of this problem. Here we stand, faced by the cancer cell, a foe so small that it cannot be seen, so tireless that it proliferates indefinitely, so relentless that it gives no quarter, so despicable that it wears no distinguishing uniform. And yet something has been learned of its nature and its methods of attack, although for about thirty centuries the last link in the chain of scientific method was lacking. Observation and hypothesis we could employ, but not experiment; only for the one hundredth part of the total period has this been available.

Etiology. It is my privilege to outline for you the present situation in cancer research, using that term in its broadest sense to include the findings of the pathologist, the clinician, the chemist, the statistician and the biologist, at least insofar as I am able to evaluate the results of those who work outside my own narrow field. A surprisingly large amount of information has been gathered, much of it negative to be sure, yet not without value nevertheless, since it permits the rejection of earlier hypotheses, and to this extent

* The Annual Gross Lecture of the Philadelphia Pathological Society.

clears the field for future investigation. Thus cancer has been found to occur rather frequently in fishes, so that it is clearly unnecessary to give further attention to soil and climate as possible causes. This in itself seems a considerable advance to one who, in the laboratory where he was working only twenty years ago, had daily before his eyes a cancer map of the British Isles picturing the distribution of cancer in respect to such physiographic features as surface water and soil. Again, the disease has been found in all other forms of animal life down to the reptiles at least, so that no more time need be wasted in examining habits and customs peculiar to man in search of a cause, except where these involve chronic irritation.

As we have been able to dismiss soil and climate from further consideration, so diet may be eliminated, in all probability, for cancer spares neither the herbivora nor the carnivora. The food that has been most often suggested as a cause in man is meat, and the suspicion arose in an interesting way. Some time toward the middle of the past century it was noticed that cancer was not so common in prisons as elsewhere, and it was proposed that this was because prisoners received less food, and less meat in particular, than more fortunate members of the community. The true explanation of the difference is now known; the average age of a jail population lies considerably below thirty-five years, the period of life at which cancer begins to appear, so that prisoners are protected by their youth rather than by enforced abstinence.

Civilization, too, often seriously advanced in the past as a possible cause, may now be disregarded, for as primitive races come more and more under observation it grows clear that they enjoy no exemption.

The one possible cause that has withstood critical examination is chronic irritation, a condition which does seem to have some real relation to the inception of malignant disease. The connection has been suspected for years, merely on observational grounds, but recently it has become possible to subject it to experimental inquiry, and this seems to me one of the greatest victories of modern medicine.

In the year 1907 Johannes Fibiger, Director of the Pathological Institute of the University of Copenhagen, was engaged in the study of tuberculosis, and in the course of his work had occasion to autopsy three wild rats. In the mucous membrane lining the prostomach of each he found an intense thickening of the epithelium, which at certain points had progressed to the formation of warty outgrowths. The process appeared to be a fibroepithelial tumor, possibly of malignant character, its cause, a parasitic worm belonging to the nematode group.

A lesion of the stomach such as this had not been previously described in rats, nor was the accompanying worm familiar to zoölogists. In order to learn something of the nature and occurrence of this unknown disorder, Fibiger examined the stomachs of

1144 rats from various sources, but found neither the nematode nor the disease which he was seeking, and he was unable to transfer the latter to other rats by inoculating or feeding the affected tissue. For most of us this would have sufficed, but Fibiger was different.

Attempts to transmit the disease by feeding experiments having failed, he began to consider the possibility that his parasite was not directly transferable from rat to rat, but required the intervention of another host. Now it had long been known that a certain cockroach (Periplaneta orientalis) is the intermediate host for a similar worm, also an inhabitant of the rat's stomach, and Fibiger, therefore, examined wild rats from a locality in Copenhagen that was swarming with this pest, but found neither nematode nor hyperplasia. Transmission experiments, also, were disappointing, for rats fed with the roach remained in good health.

A more encouraging result attended the search in rats from a large sugar refinery, where a different cockroach (Periplaneta americana) ruled. Within about nine months 61 rats were caught in this building, and in 40 of them the long-sought nematode was found, while in no less than 18 of these 40 the strange hyperplastic disease was a concomitant feature of the infestation. Rats fed with the americana, too, developed the characteristic changes in the stomach, and in some the disease actually progressed to the inception of cancer. There could no longer be any doubt that the disease depended upon the presence of the parasite or that Periplaneta americana was the intermediate host; indeed, the larval stage of the worm was easily demonstrated in the muscles of the insect. The experimental production of cancer had at last been achieved. For this, Fibiger was awarded the Nobel prize shortly before his death.

In Japan Dr. Katsusaburo Yamagiwa, Professor of Pathology at the Tokyo Imperial University, read of this work and determined to attempt once more the production of cancer with tar. The occurrence of carcinoma among those whose work exposes them to irritating substances was a clue that had inspired a long series of experiments, and in Germany, France and England the problem of inciting malignant growth in animals had been on the eve of solution at any moment during the preceding three decades, though this was entirely unsuspected at the time. The effort had failed only because an insusceptible species of animal had unwittingly been chosen or because irritation had not been continued long enough. Thus, about forty years ago Hanau, in Germany, painted rats for months with gas tar or similar materials, but elicited only a chronic dermatitis. At the close of his paper he suggested that a longer period of application might prove successful. It would almost inevitably have failed in rats, as we now know; but if he had only happened to choose the mouse for his investigation, instead of the rat, there is no doubt that he would have triumphed. The

French investigator, Cazin, made an equally unfortunate choice, the dog, and in spite of five months' tarring no carcinomas were produced. The most promising of the older experiments was that of Bayon, in England, who reported abundant epithelial proliferation, though without invasion, four weeks after the injection of tar into the ear of the rabbit. Here both soil and irritant were correctly chosen, but sufficient time was wanting. Thus do we stumble and blunder along!

In order to initiate malignant growth in animals three factors are required—an irritant, a soil which will respond to it and a sufficient length of time for the response to develop. It was the good fortune of Yamagiwa, and his collaborator Itchikawa, that in their experiments all three met at last. The word fortune has been used, not with the intent of diminishing by one iota the luster of their achievement, but because they employed the rabbit, which was chosen for no reason except that a spontaneous tumor had never been recorded on the ear, where they intended to paint; they might have taken equally well the guinea pig, which so far as I know enjoys the same freedom from tumors in this region. If they had, they would have failed with their predecessors.

However, they did select the rabbit, and soon found that tar was the most suitable among the various materials with which they began their experiments, and they possessed, furthermore, the infinite patience necessary for applying it week after week, month after month, without any prospect that their labor would be rewarded. But rewarded it was, as all the world knows, by the appearance of several carcinomas a year or so after they commenced their investigation, though the wide confirmation which was their due was delayed by the World War, and did not come until after the conclusion of hostilities.

It has long been known that sarcoma of the liver is a rather common tumor in rats, whether wild or tame, and that it occurs there in close association with the cysts surrounding Cysticercus fasciolaris, the larval form of a cat tapeworm (Tænia crassicollis). About ten years ago Dr. Bullock and Miss Curtis, at the Crocker Institute, in New York, began the artificial infestation of rats with this parasite in the hope of producing tumors under more or less controllable conditions. The attempt succeeded beyond expectation, and the experimental pathologist of today can choose among three methods of initiating malignant growth in laboratory animals, where only twenty-five years ago one seemed too much to hope for.

A moment's reflection will show that problems can now be approached upon which the transplanted tumor, an established growth composed of cells that are not autochthonous, could throw no light. Almost the first one to be investigated was the influence of age, a factor that now appears to be less decisive than had formerly been supposed, for experiment suggests that young animals

are as susceptible as older ones. Hence it would seem that the length of the period throughout which the irritant exerts its action is more important than the age of the animal when irritation is begun, so that age may be merely another way of expressing the duration of irritation.

When these experimental tumors of animals are grouped with those which follow in man the application of known irritants for a known time, such as carcinoma of the bladder in manufacturers of aniline dyes, and of the skin in the early Roentgen ray workers or in those who are daily exposed to tar, pitch and similar substances, it looks as though something like one-fifth of the life span was required for the inception of malignant disease. Thus, in the mouse, which lives for about two or three years, some five or six months of tarring is necessary; taking for man the three score and ten years allotted by the Scriptures, we should expect to find that about fifteen years would elapse between the beginning of chronic irritation and the appearance of the new growth, and it is a curious and an interesting fact that this is often true. It must not be thought, however, that the rule is anything but a rough approximation, for cases are on record where cancer has followed a splash of hot tar within a few weeks or months. Nevertheless, it is surprising to see how frequently aniline dye, tar and Roentgen ray cancer in man has come on after a period of approximating fifteen years. It may very well be, therefore, that in looking into the history of a fifty-year-old man with cancer of the stomach, we should find his habits at the age of thirty-five years more significant etiologically than his habits of yesterday, for it is now realized that neither in animals nor in man is it necessary that an irritant act continuously throughout the whole period elapsing between the first application and the ultimate appearance of the neoplasm. This matter has been studied in the tar cancer of mice by several investigators, among them Bang, who calls the time which passes between the first tarring and the occurrence of invasive growth the "developmental period," and divides it into a "preparatory period," which lasts until potential malignancy sets in, and a "latent period," which runs from the end of the preparatory period up to the supervention of invasive growth. Thus in mice painted for four months only, epithelial infiltration is rarely found at the end of this time, yet during the months following cancer appears. It is evident that latent carcinoma is present, even though no alteration in the appearance of the epithelium can be discerned under the microscope, for Murray and Woglom have shown that tarred epithelium transplanted at this stage is capable of malignant growth, and it seems as though Russell were right in his suggestion that the neoplastic change sets in suddenly, Nature departing from its common rule and moving *per saltum*—at one bound.

In order that malignant growth may be initiated, the irritant

must be exactly adapted to the soil in some way of which we are still ignorant. Tar readily elicits cancer in the skin of man, mouse and rabbit, but not in that of the dog, guinea pig or rat (Fig. 1); the connective tissue of the rat, on the other hand, is susceptible. The Cysticercus fasciolaris sets up malignant growth only in the rat, not in the mouse, in whose liver, nevertheless, it is a frequent guest; in the rat's liver it is the connective tissue which is involved, not the epithelium. In aniline dye workers, again, the kidney and ureter escape, while the bladder suffers. Most extraordinary in this series of remarkable experiences is the observation of Fibiger, that the stomach and tongue of rats respond to the presence of Spiroptera neoplastica by producing carcinoma, whereas the esophagus, invested by the same epithelium as that lining the prostomach and covering the tongue, is entirely exempt. No wonder that cancer research moves slowly!

It would be a fine thing if we could isolate from tar the portion which incites malignant growth, and many efforts in this direction have, of course, been made. Not that anyone expects to discover a specific substance possessed of unique carcinogenic activity, for it is hard to think of any factor common to tar, aniline dyes, Roentgen rays, radiant heat, the secretions of endoparasites and sunlight, all of them known or suspected to have carcinogenic powers, unless the common factor be chronic irritation. Yet while recovery in pure form of the active agent in tar might thus not put us in entire command of the situation, it would be a great achievement nevertheless, for it might then become possible to produce experimental cancer in a shorter time; or to lower the excessive death rate from tar poisoning in experimental animals; or to study the earliest stages of carcinoma unembarrassed by the concomitant inflammation set up by tar; or, most important of all, to eliminate tar cancer as an occupational disease.

The problem, however, is one of extreme difficulty, for of the several hundred constituents going to make up tar, not more than one hundred have been definitely isolated. Then, too, the composition of tar varies considerably, depending upon the coal from which it is distilled. Still, a little progress has been made, for all that, and it appears probable, for example, that the active agent is contained in those fractions coming over at a rather high boiling point, say from 250° to 500° C. and more, and that it is not arsenic, as had at first been suggested. Furthermore, it may, perhaps, be composed of carbon and hydrogen alone, though this cannot yet be definitely asserted.

If we are still ignorant of the nature of the responsible agent, we are equally in the dark respecting the way in which its effects are exerted. It cannot be through chronic irritation alone, for all irritants do not produce cancer. Thus, although chromic acid and its salts bring about lesions of the skin quite as severe as those seen

in men who handle tar, pitch and similar substances, no case of cancer has as yet appeared in dyers, tanners or bichromate manufacturers. Kennaway, who has been especially interested in this phase of the cancer problem, points out that blast-furnace tar and certain petroleums do far more visible damage to mouse skin than acetylene tar or isoprene tar, yet their application is not followed by cancer, and chlorinated acetylene tar is much more irritating than the original material, though its carcinogenic power is considerably less. Other irritants which he has found to be negative are acridine, and the product obtained from combining ethylene with phenyl magnesium bromid in the presence of nickel chlorid. We are beginning to appreciate the marvellous delicacy of the adaptation between etiologic agent and the cell which is to become ultimately a cancer cell, and to realize not only that the irritation must be of a certain kind, and perhaps, also, of a certain degree, but also that there may be more factors involved than chronic irritation simply as such.

Characteristics of the Cancer Cell. That we have not the slightest conception of what these may be you need no one to come a hundred miles to tell you. Study of the morphology of the cancer cell reveals nothing except that it is a wolf in sheep's clothing, for no constant difference has been found between it and any other young, actively growing cell, unless, indeed, the investigations of Lipschütz may eventually throw some light on the situation. This writer has described a "plastin reaction" in the cells of various tumors, a basophilic mass lying in the cytoplasm to one side of the nucleus in the form of a hood, or cap, which he believes to represent an optical demonstration of the change undergone by a normal cell in becoming malignant. The work is still so recent, however, that there has not yet been time for others to repeat the investigation.

The chemistry of the cancer cell, dead or living, has long been a subject of inquiry, in the hope that some deviation from the normal might be discovered which would give a clue to its nature and perhaps even suggest some means of putting an end to its activities without detriment to the rest of the body. Needless to say, no such difference has yet been found.

In this connection the experiments of Warburg and his collaborators come at once to mind. Their starting point was the fact that the respiration of sea urchin eggs increases sixfold at the moment of fertilization, and it was thought that a similar acceleration of respiration might occur in the transition from resting epithelium to carcinoma. The respiration was, therefore, measured in thin slices of the Flexner-Jobling rat carcinoma kept in Ringer solution at body temperature, and compared with that of kidney and liver, when the astonishing fact emerged that the respiration of the carcinoma was not greater than that of the two normal tissues, as it had been supposed would be the case, but considerably less. This

result was so startling as to justify the assumption that the tumor lacked suitable material for combustion, and various nutritive substances—amino-acids, fatty acids and glucose—were, therefore, added to the Ringer solution with the expectation that the respiration of the tumor cells would now increase. But the result was not as anticipated; amino-acids and fatty acids had no effect, while glucose brought the respiration to a standstill. In trying to discover why this should be so, Warburg found that lactic acid appeared in the Ringer solution as a result of glycolysis, and that this inhibited respiration. Liver and kidney produced only very small quantities of lactic acid, and as it was thought that this glycolysis might perhaps be a characteristic feature of the cancer cell, a thorough investigation of its glycolytic activity was instituted.

Many cells have the power to split 1 molecule of glucose into 2 molecules of lactic acid in the absence of oxygen, but as oxygen does affect glycolysis a sharp distinction must be drawn between glycolysis under anaërobic conditions and glycolysis under aërobic conditions. In the presence of oxygen the simple splitting metabolism is decreased or abolished in the case of muscle. Carcinoma was found to behave like yeast, its respiration being a combined oxidation and splitting metabolism rather than a pure oxidation metabolism such as that of muscle.

Further investigation, however, both by Warburg and by others, showed that this mixed respiration is not entirely characteristic of malignant growth, being shared by some normal tissues, while Murphy and Hawkins were unable to discover the slightest suggestion of correlation between the clinical behavior of animal tumors and the type of respiration exhibited. A regressing transplanted tumor containing almost nothing but connective tissue might respire like an actively growing one composed entirely of healthy tumor cells, while most of the spontaneous neoplasms investigated resembled benign growths in respect to their respiration, although they fulfilled all the criteria of malignancy in their biologic characteristics.

The practical value of Warburg's hypothesis is now being tested in Germany, where combinations of oxygen with other agents are being administered to hopelessly inoperable cancer patients, in the hope that splitting metabolism may be checked and the cells of their tumors restored to the normal course once more.

Innumerable other attempts to find some difference between the cancer cell and its normal prototype have led to nothing but disappointment, and I can find no constant difference in the literature which all agree to be characteristic of the malignant cell. Salt metabolism, surface tension, isoelectric point, glutathione, proteins, fats, carbohydrates, vitamins, enzymes, insulin, light of various wave lengths, arsenic, dyes, have all been investigated—and I have so far gone only through the D's in my card index of authors. How many others there are I shall leave to your imagination, stop-

ping only to mention hydrogen-ion concentration, since this, perhaps, has attracted the most attention. Between 1906 and 1921 it was reported by six different observers that the blood of cancer patients was more alkaline than normal blood, and by now the question has been under discussion for twenty-four years, yet without a unanimous opinion having been reached. In the most recent article known to me it is said that no significant difference could be found in the serum between patients with early malignant disease and a group of noncancerous persons.

About six years ago I tried to find out whether there was any difference between the pH of the cancer cell itself and that of other cells in the body, and came to the conclusion that if there were any it was too small to be appreciable by even the most careful potentiometric measurement of cell extracts. Since then the work has been repeated by five other investigators, some of whom have professed themselves at a loss to understand how any such conclusion could have been reached and have kindly explained all my mistakes. But as two of the five found the cancer cell acid, two more declared it alkaline and the fifth said that it was at first acid and later alkaline, my confidence in their findings is not so strong as I should like to have it.

When all is said and done, the only constant characteristic of the cancer cell so far discovered is its egoism—a sort of impudent independence which we cannot weigh, measure or explain. This manifests itself not, as is so often said, in rapid growth, for bacteria and the cells of the embryo leave the cancer cell far behind in this respect, but in a remorselessly steady proliferation, the commands of the body to stop, if, indeed, any are issued, being entirely disregarded, by the ordinary spontaneous tumor at any rate. Tar cancer, on the other hand, whether in man or in animals, has not quite this independence, but recedes more often than we think it should when its morphology is taken into consideration. Whether this cure is a spontaneous gift on the part of the cancer cell, or a concession reluctantly won from it by the activities of the body, none can say.

Immunity. In the case of the transplanted neoplasm the latter is the case. Tumors of this group disappear spontaneously with great frequency, though for years the reason was not understood. It was known that animals in which a growth had been cured were often immune against further inoculation, but the cause of this exemption was by no means clear. The immunity might have preceded and caused the cure, or, on the other hand, the tumor might have regressed for some reason connected with its own metabolism and then, during its absorption, elicited immunity in the host. Defendants of either hypothesis could be found, though perhaps the former was the more preferred. I venture to think that some work of my own shows it to be the correct one.

The areas of a number of growing or receding Jensen rat sarcomas

as charted were measured with a planimeter and plotted against time. The resulting curves showed that those tumors which were eventually to recede were at a disadvantage, compared with those that were to grow, soon after the end of the first week following transplantation, the growth curve of receding tumors crossing that of growing ones at about the tenth day. It was then necessary to inquire why the receding Jensen sarcoma should fall behind the others at this, rather than at any other, time. It has been known for many years that immunity to propagable neoplasms is at its height about ten days after introduction of the agent employed to elicit it—blood, embryo skin or whatever has been chosen, and it was, therefore, suspected immediately that immunity was at the bottom of this retardation of the growth curve at the tenth day. To show whether or not the suspicion was justified, a group of rats was inoculated with the Jensen sarcoma and reinoculated with it on the opposite side three, five, seven and so forth days after the first implantation. As Russell had shown that this sarcoma immunizes the host during its growth, it was expected that these rats would prove increasingly refractory to the second inoculation from day to day and that the height of their resistance would be reached on or about the tenth day. The expectation was realized, immunity rising from about 60% on the third day to 100% on approximately the tenth.

So far, of course, nothing more had been proved than that regression of the Jensen sarcoma sets in at the time when the refractory condition reaches its full development. To show that cure is a result of this immunity and of nothing else, other evidence had to be sought. If it really be the host which determines regression, and not some sort of alteration in the vitality of the Jensen sarcoma itself, it might be anticipated that in an animal with bilateral tumors resulting from simultaneous inoculation regression, if it occurred at all, would affect both nodules and at about the same time. This proved, in fact, to be so, for no example could be found of a regressing Jensen sarcoma in one axilla and a progressively growing one on the opposite side, among the double simultaneous inoculations that had been made with this tumor at the Crocker Institute.

Not to labor the point, the investigation was continued until all possibilities that could in any way be ruled out had been eliminated and it was possible to conclude that cure of the Jensen sarcoma is accomplished by the immunity which this tumor engenders in its host. In other words, the tumor digs its own grave, as Apolant said so many years ago in another connection.

The knowledge that tumors resulting from bilateral simultaneous inoculation pursue the same course, succeeding or failing together, gave an opportunity to investigate the very earliest phases of regression, for it was necessary only to inoculate a number of rats in both axillæ and to remove one tumor from each animal at appro-

priate intervals, leaving the other *in situ* for observation. Thus, there was available for comparison a series of slides from tumors which would have grown had they remained in the host, and another from tumors that would have disappeared. Until then, only such tumors as had already begun to decrease in size were available for the study of regression, and the process is by then so far advanced that there had been considerable difference of opinion in respect to the point at which the tumor is earliest affected, some investigators maintaining that the margin is the first to suffer, and others that the primary changes occur in the central portion.

Study of a series of slides (Fig. 2) prepared in the manner just indicated showed that the first discoverable alteration in Jensen tumors that were eventually to regress was the appearance of a narrow zone just beneath the capsule, and some 6 to 12 cells in width, where the cytoplasm (in eosin-hematoxylin preparations) was definitely more pink than in other parts of the section, and somewhat swollen. Most of the nuclei in this zone were pale and small, as if undergoing chromatolysis; a few retained the normal size and appearance, and mitotic figures were not rare, though only about half as frequent as in other portions of the slides examined. If the cells in this pink zone were largely moribund they had not all been attacked with equal success at the same moment, as the presence of some normal nuclei, and even of mitotic figures, amply demonstrated.

The next stage was the appearance of a peripheral zone of undeniable necrobiosis, with a band of fibrosis immediately outside it and apparently derived from the capsule. The cell death and the replacement fibrosis, if such this may be called, drew gradually inward until the tumor had been converted into a fibrous mass. It seems hardly necessary to say that the marginal necrosis now under discussion is a process entirely distinct from the central necrosis which affects almost all transplanted tumors, be they growing or receding, and which seems to have nothing to do with spontaneous cure.

Destruction of the Jensen sarcoma seems to begin at the periphery, then, the lethal agent, or condition, gradually permeating the neoplasm and killing its cells one by one. The fibrosis, so often regarded as the essential part of the process, is very likely not there to strangle the tumor cells but merely to replace the defects left by tissue that has already been killed. Throughout the healthy parts of the tumor inside the marginal necrobiosis the cells immediately surrounding the capillaries appeared to be normal; hence the lethal principle, if present in the blood stream, must either be there in negligible quantities, or else be incapable of passing out through a single layer of endothelium. The fact that the first changes occur where tumor cells are in contact with the capsule, even where this penetrates parenchyma in the form of trabeculæ, suggests that the destructive substance, or condition, is associated in some way with

the connective tissue which surrounds the tumor and enters it to form the stroma.

It is necessary to refer in the vaguest manner to this deleterious principle in immune animals, for no clue to its nature has yet been discovered, in spite of the most painstaking search; certainly there is no reason to affiliate it with any of the known antibodies for no qualified observer has found a precipitin, a cytolysin, or any other of the antibodies which accompany bacterial immunity, and it has proved, in truth, a bitter disappointment. At the present time there is no sign that immunity will ever be of any practical help. There are two reasons for thinking so: (1) It is active only against a newly implanted graft, having no power over an established tumor; (2) even though it were able to conquer a transplanted new growth, it would have no effect, or so we believe, upon a spontaneous neoplasm, for Haaland has shown very clearly that an animal cannot be immunized against a tumor arising from its own cells.

Diagnostic Tests.—It is this close relationship between the cells of a spontaneous tumor and those of the rest of the body in which it has its being, that makes the search for a diagnostic reaction such a thankless task. A cancer the size of a small pea, say, would weigh perhaps 0.1 gm., thus representing but $\frac{1}{700,000}$ part of the body weight of a 70-kilo patient. And this 1 part in 700,000, furthermore, is not made up of totally different material, such as the typhoid bacillus; on the contrary, it and the rest of the body are as much alike as two Ford cars.

It is this very similarity that delays, also, the discovery of a specific cure. This must be some agent which will destroy the tumor without inflicting on the rest of the body, during the fray, the traditional fate of the innocent bystander. But, in addition, it must be able to exert its effect after subcutaneous or intravenous injection, as antitoxin does in diphtheria, or more happily still, after administration by mouth, for cancer so often involves a remote organ that a remedy which had to be introduced directly into the growth would hardly be worth the trouble of preparing. Almost every conceivable substance has been tried and found inoperative, and a pessimist might almost be excused for saying that we know at present more things that will not kill the cancer cell than we have ever known before. Lead has a few miracles to its credit, but many, many more failures, and is still in the experimental stage. Radiotherapy, of inestimable value for its mitigant action, may even be curative in certain cases, but only in certain cases. The surgeon, powerless to untie the Gordian knot of cancer, boldly cuts it, and this modern Alexander is after all our mainstay now, as he has been in the past.

Conclusion. In conclusion, I would submit that the situation is grave, yet not hopeless. Years ago, in a spirit of good-natured mockery, the Director of our Institute appointed me its official

FIG. 1.—Tar cancer in the rat—a unique tumor—produced by Dr. Herly at the Crocker Institute.

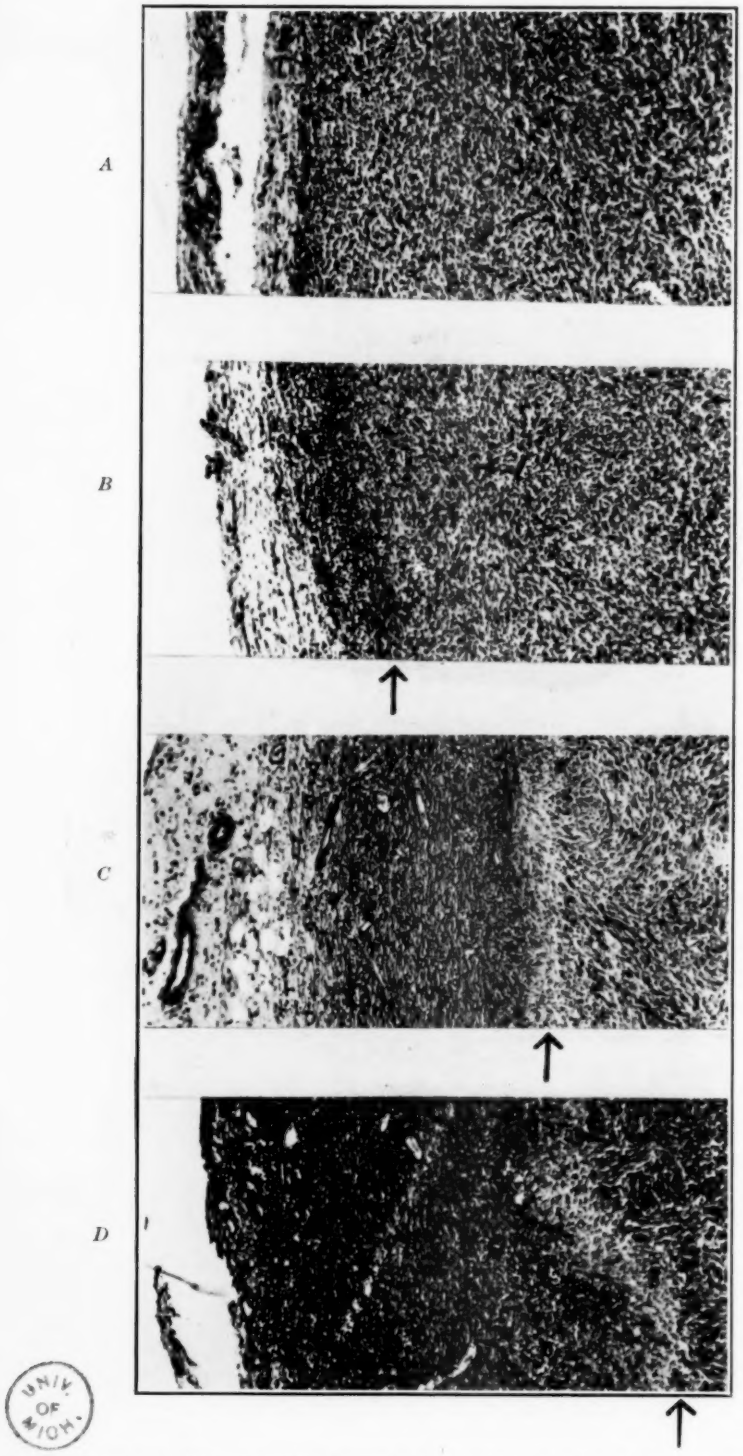

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FIG. 2.—*A*, healthy growing Jensen rat sarcoma. *B*, *C*, *D*, three early stages in the regression of this neoplasm. The arrows show the zone of dying tumor cells described in the text.

FIG. 3.—Portrait of Professor Johannes Fibiger. (Courtesy of Scientific Monthly.)

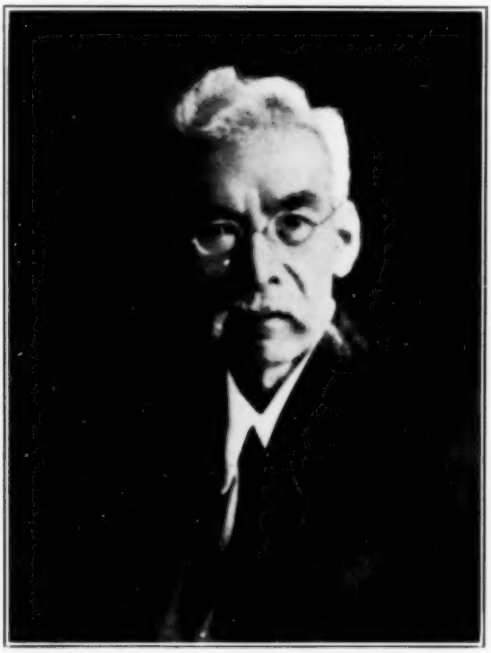

FIG. 4.—Portrait of Katsusaburo Yamagiwa. (Courtesy of Journal of Cancer Research.)

optimist, but I am able to hold that position solely because I have accustomed myself to look for advance decade by decade rather than year by year.

An experimental approach to the problem of malignancy has been available for only thirty years; yet please remember that before the end of the first ten-year period the limits within which malignant tumors can be transplanted had been mapped out, a method of protecting against their inoculation found, the resistance of the cancer cell to various agents compared, its cultivation *in vitro* begun, the hereditary nature of cancer in mice foreshadowed and a curiously interesting transmissible sarcoma of the fowl discovered and described.

In the second decade the growth rate of the cancer cell was assessed, and two methods of producing tumors in animals were discovered, although it had been said that this would never be accomplished, and in spite of the fact that this period was disrupted by a world-wide war.

In the third, still another means of inciting malignant growth was reported, and a good start made on such problems as the chemical nature of the carcinogenic agent in tar, the intensity and duration of irritation required to initiate neoplasia, the relation of age to the development of cancer, and so on, while positions gained during the first two decades were consolidated and extended. I cannot but believe that in this experimental period of thirty years, representing only 1% of the three thousand years during which cancer has been under observation, vastly more than 1% of our present knowledge of cancer has been acquired.

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES. II. PLASMATOCYTOMATA AND THEIR RELATION TO MULTIPLE MYELOMATA.

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The classical multiple myeloma, first described under the term "mollities ossium" by Macintyre in 1850, is confined in many cases to the bone marrow and for this, if for no other reason, is often

classed among the bone tumors (Borrmann). It is described by Ewing (1928) as a "specific malignant tumor of the bone marrow arising probably from a single cell-type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria, and a fatal termination." Other cells have been described as composing the tumor (Witzleben, 1925), (Helly, 1927 lit.), but we are here concerned with the plasma-cell type only.

While very generally regarded as a bone-marrow tumor, (Borrmann, 1900), (Aschoff, 1911), (Ewing, 1928), some pathologists are inclined to regard the disease as more closely allied to the leukemias and thus as a disease of the blood-forming organs in general. Witzleben (1925) believes that multiple myeloma should be classed as a disease of the hemopoietic system, aleukemic in nature with predominating participation of the bone marrow, but involving not rarely of other blood-forming tissues. Pappenheim (1907. 1) states that "multiple myeloma is not a disorder peculiar to the bone marrow but is, like leukemia and pseudoleukemia, a generalized disease of the whole hemopoietic system which happens to affect at first or primarily the bone marrow." Lubarsch (1906) holds virtually the same views and believes further that myeloma is a hyperplastic rather than a neoplastic disease. At present we are more concerned, however, with the question whether the condition is a generalized disease of the hemopoietic system or not, rather than whether it is a neoplastic or a hyperplastic process.

Various considerations support the view that multiple myeloma is a system disease not necessarily confined to the bone marrow. Generalized diffuse myelomata have been described by Berblinger (1911), Schmidtmann (1921), Helly (lit. 1927), and Enneking (1928), and it is common experience that the tumors may be multiple and discrete or diffuse to a greater or less extent. One of our cases seen with Dr. J. H. Shortell showed nodular involvement of the head of the humerus and diffuse replacement of the shaft of the same bone. Neither portion gave the usual Roentgen ray picture of multiple myeloma, yet pathologic section was characteristic of the disease and typical discrete lesions were present in the ribs. Extra-osseous metastases have been described by several authors (Hoffmann, 1906), (Maresch, 1909), (Bertrand, Soupault and Gutmann, 1927), (Battaglia, lit. 1928), (Geschickter, lit. 1928), and would appear not to be excessively rare. Amersbach and Schridde (1909, quoted by Vogt, 1912) describe a case with multiple involvement of the bones, splenic tumor, and enlargement of the cervical, axillary and peritracheal nodes. Plasma cells were the characteristic tumor cell and were also found in the blood. In our series of cases extra-osseous involvement occurred in 2 out of the 17 classical cases, and in one of the plasmomata primary in a lymph node.

Plasma cells have been described in the blood from cases of apparently typical multiple myeloma (Beck and McCleary, 1919), Ghon and Roman, 1913); while Piney (1924) has described plasma-cell leukemia with involvement of the spleen, liver, ribs, sternum and spine. He was unwilling, however, to class the case as multiple myeloma, because the process was diffuse and because there was no Bence-Jones protein in the urine. But as Lubarsch points out, neither extra-osseous foci nor diffusion of the process should militate against the diagnosis of myeloma, and Bence-Jones proteinuria is by no means a constant finding in the disease. In none of our cases of typical multiple myelomata in which the blood was carefully examined did "tumor" cells occur. In 2 cases myelocytes were occasionally seen. In 2 the monocytes were consistently above 10 per cent during the entire course of the disease. Otherwise no abnormalities were noted in the blood white-cell series. In none were abnormalities in the blood platelets noted.

Plasmocytomata entirely outside the osseous system have been repeatedly described (Sternberg, 1926), (Vogt, 1912), (Bourgeois and Heut, 1929), (Hertz and Mamrot, 1913). There are two such instances in our series.

Thus there appear in the literature cases of both extra-osseous and intra-osseous plasmocytomata. The question still remains, however, whether classical multiple myeloma should be classed as an intrinsic disease of the bone marrow or as a disease of the hemopoietic system in general, capable of involving extra-osseous structures and possibly even arising in them. We have chosen 5 cases from our series of 17 because they appear to throw additional light upon this interesting and not entirely academic question.

Case Reports.—Case I. E. K. (H. H.–21–1118), a married Norwegian painter, aged forty-six years, entered the Collis P. Huntington Memorial Hospital on September 21, 1921 complaining of a recurrent growth in his throat.

During the early years of his life he had been, in general, very healthy and he remembered no childhood diseases.

In 1918, three years before entry to the Huntington Hospital, he had a painless tumor removed from the left tonsillar region at the Massachusetts Charitable Eye and Ear Infirmary.

First Biopsy. The pathologic report on this specimen (M. G. H., February 6, 1919) was: "A tumor about 2¼ inches greatest diameter partly invested with mucosa and with some muscle tissue adherent. On section, it is composed of soft, grayish tissue. Microscopic examination shows the tumor to consist of closely packed cells and very little stroma. The cells are generally small and have indistinct scanty protoplasm. They seem to belong to the lymphocyte series and are atypical. Only one mitotic figure found. There is some infiltration of the muscle by tumor cells." (Fig. 1.)

Diagnosis. Lymphoma, probably of low-grade malignancy.

Second Biopsy. A year later a similar mass was removed from the right side of his throat (Brooks Hospital, January 27, 1920). The pathologic report follows: "This is a small, definitely circumscribed mass, made up chiefly of small round or slightly elongated cells, probably of the lymphocyte

series. It is evidently of very slow growth as no mitotic figures could be found. There is evidence of inflammatory reaction about the periphery. It may be a slowly growing lymphoblastoma. There is also a possibility, though this seems remote, of myeloma. An examination of the urine for albumose might help in diagnosis."

We have been able to examine the microscopic sections from this biopsy specimen and the histologic picture is identical with that of his third biopsy specimen described below.

After these operations he remained symptomless until eight months before entry to the hospital. Shortly before that time (January, 1921) he again noticed an obstructive tumor in his throat and the right side of his neck became swollen. The tumor in his throat grew rapidly and was of sufficient size to cause some obstruction to swallowing. There were, however, no general symptoms and his general physical condition was excellent.

On entry, the right tonsillar region was found to be occupied by a smooth, firm spherical tumor measuring 3.5 cm. in diameter. The remainder of the physical examination was normal. He weighed 175 pounds. The white blood cell count was at the time of admission 8200 per c.mm. and the differential showed 65 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 28 per cent lymphocytes and 5 per cent monocytes. No abnormal or young cells were seen. The red blood cell count was normal but the red blood cells were slightly achromic. The urine was negative.

A clinical diagnosis of lymphosarcoma was made and three radium seeds, of 2 m.c. each, were inserted deep into the tonsillar mass. Under this treatment the tumor receded markedly in size. There were no signs or symptoms pointing to generalized involvement.

The patient remained symptomless and apparently healthy for the next five years.

On January 15, 1926, eight and a half years after the removal of the first tumor, the patient again presented himself at the Clinic with the complaint that for the past three months he had been troubled by pain in the right sacroiliac region and a steady, boring pain radiating down the outer side of his right leg and into the foot. For the past few weeks he had also had a dull, continuous headache in the frontal region.

Physical examination at this time showed him to be well developed and nourished. There was a small ulcer just above the epiglottis, presumably an aftermath of the former radium treatment. The original tonsillar tumor had not returned. There were no palpable lymph nodes in any region. No abnormalities were found elsewhere. The blood at this time showed a red cell count of 3,950,000 per c.mm. with a hemoglobin of 95 per cent. There were 11,800 while blood cells per c.mm. with 75 per cent polymorphonuclears, 14 per cent lymphocytes, and 11 per cent monocytes. The urine was entirely normal. A Roentgen ray film of the lumbar vertebræ and the sacroiliac regions showed no abnormalities other than slight hypertrophic changes such as might be seen in any man of his age. Acting on the belief that the pain was due to enlarged metastatic retroperitoneal lymph nodes, a full suberythema dose of Roentgen ray was given over the sacroiliac region and another a month later. Following this second treatment there was marked relief from the pain. The patient remained symptomless until March, 1926. At this time, examination of the throat showed once more a bulging of the left tonsillar fossa and bean-sized lymph nodes, soft, discrete and freely movable, in the right posterior cervical chain. There were, however, no symptoms of importance.

In May, 1926, he returned to the clinic complaining for the first time of sharp pain in the left chest. There was some tenderness in the seventh interspace in the anterior axillary line. Nothing abnormal, however, was found by the Roentgen ray, though a few crackling râles were heard on inspiration at the bases of both lungs. There was no friction rub. Two days

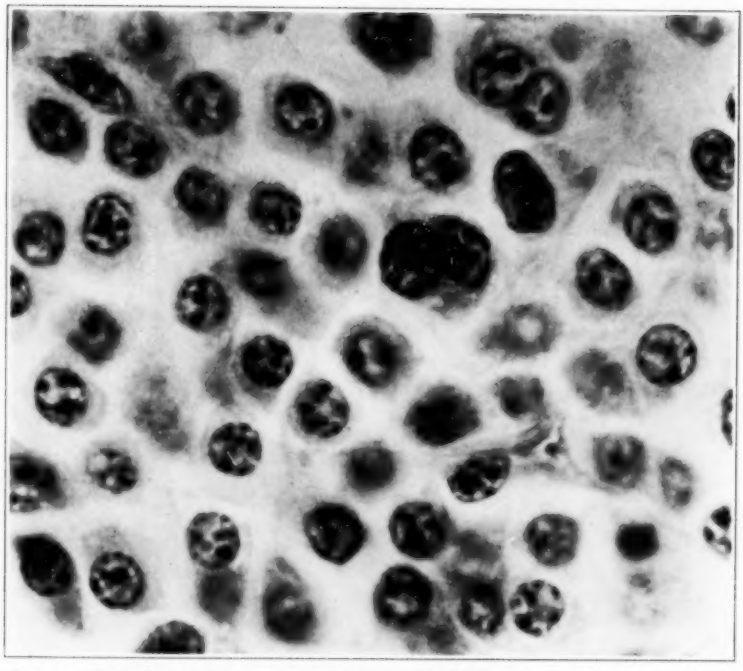

FIG. 1.—Tonsillar tumor removed February 6, 1919. Eosin methylene blue. × 1500.

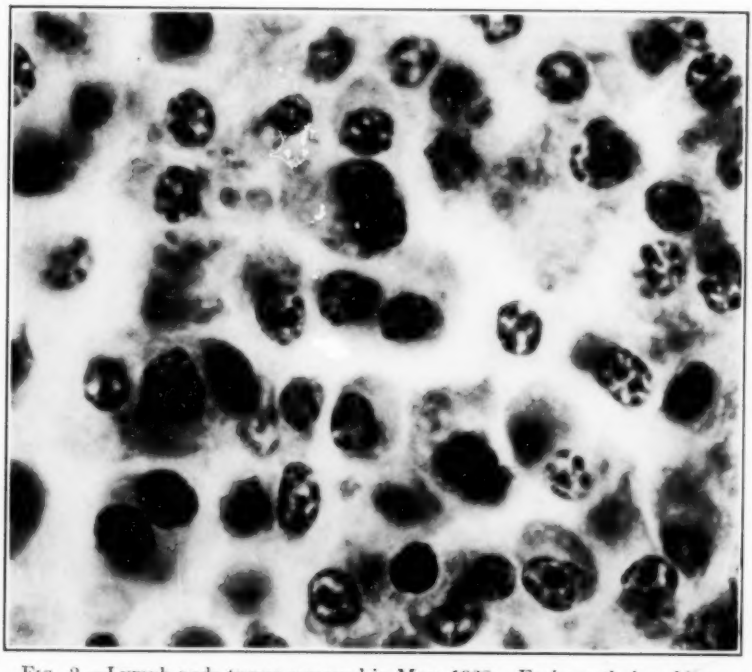

FIG. 2.—Lymph-node tumor removed in May, 1928. Eosin methylene blue. × 1500.

later he fell from a step ladder, striking his left chest. There was tenderness over the tenth rib near the spine, and Roentgen ray showed a fracture of this rib but no other abnormalities. This fracture healed; the pain in the chest disappeared completely, and it was not until October, 1926, that he returned to the clinic. The pain in the chest had returned and there was a loose, troublesome cough. Bence-Jones protein was, for the first time, noted in the urine. The blood picture remained essentially normal except for a slight secondary anemia. Roentgen ray examination of the chest showed for the first time, eight and a half years after the initial throat tumor, circular areas of diminished density throughout the ribs and pelvis, suggestive but not entirely characteristic of multiple myeloma. He received one-half an suberythema dose over the anterior chest and the pain entirely subsided. There followed an eight-month interval, during which he remained free from symptoms except for an occasional cough.

In June, 1927, the cough became more severe and there was a constant aggravating pain in the right posterior chest. A moderate amount of dyspnea was also complained of for the first time. The lungs showed on examination slight dullness at both bases with fine crackling râles. The urine contained much albumin and a few granular casts. The Roentgen ray films taken at this time showed numerous small rounded areas of diminished density in the ribs, skull, ilium, and right and left femurs. The white blood cells remained essentially normal, but the red blood cell count had fallen to 2,640,000 per c.mm. and the hemoglobin to 66 per cent. A full suberythema dose of Roentgen ray was given over the chest, both front and back, and in a week the pain in the chest had disappeared, though the cough and dyspnea to a large extent remained. The patient remained essentially symptomless except for an occasional cough and some troublesome, but not severe, pains in the lower back and chest, which persisted until his death.

In January, 1928, he again received a full suberythema dose of Roentgen ray over the chest as the pain and cough had increased. This treatment to a certain extent relieved his symptoms but the râles and dullness persisted at both bases.

Third Biopsy. In May, 1928, a lymph node was removed from the left neck (S–28–1256). (Fig. 2.) The pathologic report follows: The specimen consists of several fragments of reddish brown tissue, irregular in shape. The largest measures 1 cm. by 0.5 cm. by 0.5 cm., and the smallest 0.5 cm. by 0.5 cm. by 0.3 cm. On section, the tissue cuts with difficulty. Microscopic examination shows the normal structure of the lymph node is completely lost due to a diffuse infiltration with tumor cells. Only in a few areas can small focal collections of lymphocytes be distinguished. At several points at the periphery, the tumor cells have invaded the capsule and are growing in the surrounding fat and connective tissue. The tumor cells are polygonal or stellate in shape and are somewhat larger than small lymphocytes. Their cytoplasm is basophilic and contains, near the nucleus, a small clear area in which can be seen the centrosomes. Their nuclei which are eccentrically placed are round with a thick nuclear membrane and heavy masses of chromatin often arranged at the periphery. A considerable number of the cells are binucleate and some contain three and four nuclei. In general, the cells do not vary much in size but an occasional large cell with a correspondingly large nucleus can be found. Mitotic figures are present but are extremely rare. Scattered among the tumor cells are a few macrophages, containing blood pigment.

Diagnosis. A slowly growing plasmocytoma.

Supravital studies employing as stains neutral red and janus green were also made on this specimen. The tumor cells appeared as medium-sized, polygonal cells with eccentrically placed nuclei. The nuclei contained large

masses of chromatin. The cytoplasm of the cells had a slightly brownish tinge and showed many rod-shaped mitochondria, especially in the neighborhood of the nucleus. The cells contained few or no neutral red granules. These cells were identical with those of a myeloma of the humerus studied in the same manner.

Smears of the lymph node were also made and stained with Wright's stain and with Sato and Sekiya's peroxidase stain. In the preparations stained with the former the tumor cells looked like typical plasma cells. They gave a negative peroxidase reaction.

At this time his red blood cell count was 2,380,000 per c.mm.; hemoglobin, 60 per cent. The white blood cell count was 9150 per c.mm. with 82 per cent polymorphonuclears, 2.5 per cent eosinophils, 2.5 per cent basophils, 5 per cent lymphocytes, and 9 per cent monocytes. There was apparent some loss of weight. For the first time he seemed to be definitely losing ground. He had become quite weak, the cough was aggravating, and came in paroxysms, which were most painful and which could be controlled only by codein. Dyspnea was constant though not marked. There was slight pitting edema of the ankles. Bean-sized lymph nodes were found in the left and right posterior cervical chains, and in the right axilla. They were soft, discrete, freely movable, and nontender. No tumor was apparent in the throat. The lungs showed dullness and râles at both bases. The liver was just palpable on gentle inspiration. The spleen could not be felt.

By August, 1928, the anemia had become more severe. The red blood cell count was 2,190,000 per c.mm., the hemoglobin, 43 per cent. A diffuse brownish pigmentation had appeared all over the body, especially on the face and neck. There was extreme pain in the left posterior axillary line at the eleventh rib, with tenderness over the same area. The pain in the left hip and leg had returned in aggravated form. Walking was impossible without a cane. There was marked loss of weight. A full dose of Roentgen ray was given over the sacroiliac region, but the relief was trifling. He never was able to walk with ease again and the pain, though not severe, was constant. His cough returned and could be controlled by codein only.

In October, 1928, he had a severe nosebleed from the right nostril, for which no further cause could be found than a small ulceration on the septum. This bleeding continued intermittently until his death, though it was never severe enough to aggravate his already existing anemia.

In January, 1929, he had become much weaker. Pallor was striking and cachexia marked. The brownish pigmentation of the skin appeared more noticeable, perhaps because of the increasing pallor. The superficial lymph nodes in the axillæ and neck did not increase in size. A few râles and some dullness were still present in both bases of the lungs. The liver reached 8 cm. below the costal margin but the spleen could not be felt. There was well-marked pitting edema of the ankles. The urine continued to show albumin in large amounts, Bence-Jones protein and many finely granular casts. An occasional red cell was seen. The temperature was normal. The white cells numbered 5620 per c.mm. with 67 per cent polymorphonuclears, 3.5 per cent eosinophils, 1.5 per cent basophils, 10.5 per cent lymphocytes, and 17.5 per cent mononuclears. The red blood cells were 2,000,000 per c.mm. with a hemoglobin of 43 per cent. A two-hour renal-function test showed fixation of specific gravity at 1010 with a day excretion of 1200 cc. and a night urine of 1100 cc. The blood nonprotein nitrogen was 36.8 mg. per 100 cc. He was so weak that he was admitted to the hospital. On entrance breathing was slow and stertorous. He was drowsy most of the time but no abnormal neurologic signs were elicited. The scleræ were icteroid. The heart was normal. The blood pressure was 142/80. The lungs showed dullness at both bases with many fine crackling râles. The liver was palpable 4 cm. below the ribs. He gradually became more drowsy

and could be roused with difficulty. The blood nonprotein nitrogen rose to 130 mg. per 100 cc. He gradually became worse and died on February 2, 1929, ten and a half years after the removal of the first tumor.

Autopsy. Autopsy (H. H. 29–338) showed multiple myeloma involving the ribs, right radius and lumbar vertebræ, hypertrophy and dilatation of the heart, generalized arteriosclerosis, chronic nephritis. All the ribs showed at one or more places fusiform enlargement. On section these enlarged portions were found to consist of a thin, bony shell enclosing a cavity filled with soft, fleshy red tissue.

Microscopic examination of a section of a rib showed the following: The marrow cavity is filled with tumor cells of the same type as described in the preceding lymph-node biopsy (S–28–1256).

No normal marrow cells can be made out. The cortex of the bone shows marked thinning and at one place the tumor has broken through and is invading the adjacent striated muscle.

Case II.—M. R., a married man, aged fifty-three years, entered the Boston City Hospital in April, 1929, complaining of a lump in his neck. In addition, for "some time" he had had pain in his left hip. The past history was entirely negative. Roentgen rays of the bones showed only hypertrophic changes in the left hip joint. There was a moderately hard, freely movable mass low and anteriorly in the right neck. This was removed and proved to be a plasmocytoma (S–29–1186), histologically identical with the tumors removed from Case I. Two months later the pain in the leg was much more severe, and Roentgen rays then showed a few small circular areas of destruction in the left iliac crest and left femur. There was no anemia, no abnormalities in the white cells, and the urine showed a small trace of albumin, but no Bence-Jones protein. The blood pressure was normal. A month later the bone lesions demonstrable by Roentgen ray had spread to the ninth dorsal spine, and bean-sized lymph nodes, soft and freely movable, had appeared on both sides of the neck, both anterior and posterior to the sternomastoid muscle. The pain in the leg became more severe.

In August, the pain in the right hip and leg was more severe and he was unable to walk. There was exquisite tenderness over the right sacro-iliac joint. At this time Roentgen ray showed several small, sharply defined areas of destruction in the skull, ninth dorsal and third lumbar vertebræ, and in the ninth and tenth ribs. There were irregular areas of destruction in both iliac crests and the left ischium. The findings were considered by the roentgenologist more characteristic of metastatic malignancy than of myeloma. Bence-Jones protein was found for the first time in the urine. High voltage Roentgen ray treatments were given with but slight improvement. The patient continued to have considerable pain, however, and subsequent Roentgen rays showed a spread of the lesions. In October, 1929, the patient was considerably worse. There was marked loss of weight and a definite secondary anemia. The red blood cells were 3,000,000 per c.mm., the hemoglobin 65 per cent. The white blood cells were 5200 per c.mm. The differential count showed 68 per cent adult polymorphonuclears, 7 per cent young polymorphonuclears neutrophils, 1 per cent eosinophils, 10 per cent lymphocytes, and 13 per cent monocytes. Roentgen rays demonstrated a marked spread of the bone lesions. The pain in the hip and leg became progressively worse. The lymph nodes in the neck enlarged considerably and there appeared in the right-mid-abdomen a progressively enlarging firm mass reaching the size of a grapefruit. It appeared to be retroperitoneal, but was not fixed. Enlarged lymph nodes appeared in both groins. The patient became increasingly weaker and died in November, 1929. Unfortunately, no autopsy could be obtained.

CASE III.—A. O., a married woman, aged sixty-seven years, entered the Carney Hospital on July 17, 1927, complaining of a mass in the neck.*

The past history was essentially negative.

Six months before entry the patient noticed a small, painless mass beneath the left ear. This increased in size and was accompanied by sharp pains radiating down the side of the neck and to the left occipital region. On entrance there was found in the left neck posterior to the sternomastoid muscle a freely movable, firm, walnut-sized tumor. No other masses were noted. There was a marked secondary anemia with a red cell count of 2,560,000 per c.mm. and 30 per cent hemoglobin. The white cell count was 5000 per c.mm. and the differential count was normal. The mass in the neck was excised (S–28–1706) and proved to be a plasmocytoma identical histologically in all respects with the tumors removed from the other 2 patients. The urine showed a trace of albumin. Roentgen rays of the bones, however, showed no involvement and there were no symptoms suggesting classical multiple myeloma. There was an uneventful recovery from the operation and the patient was known to be well and symptomless nearly three years later. No local recurrence has been noted.

CASE IV.—C. F., a male aged sixty-four years, entered the Pondville Hospital on February 28, 1929 (No. 1183). The past history was negative. One sister had died of "cancer."

Two years before entry a small, soft lump appeared on the anterior surface of the upper gum. The mass was treated with radium and temporarily disappeared, but a few months later he noticed that his upper lip and right side of his nose were being pushed out. Since that time the tumor gradually grew and at the time of entrance to the hospital was of sufficient size to cause some obstruction to breathing.

Complete physical examination on entrance was negative except for a blood pressure of 220/120 and a moderately enlarged heart. There was a soft tumor partially replacing the upper alveolus, extending forward onto the upper lip and backward one-third the distance of the hard palate. The nasal septum was pushed to one side and the tumor mass nearly completely blocked the posterior nasal opening. There were no enlarged lymph nodes nor any abdominal masses. Under colonic ether the mass was removed almost in its entirety. It proved to be a plasmocytoma (H. S. 29–1503).

The urine was negative. There was no anemia and the white blood count was normal. Roentgen rays of the skull, pelvis, femora and ribs showed no evidence of malignant disease. Nine months later there was no local return of the tumor and the patient felt entirely well. The blood pressure remained markedly elevated, and the urine normal. In April, 1930, he died suddenly at home, probably from cerebral hemorrhage. No autopsy was obtained.

CASE V.—D. S., a truck driver, aged fifty-one years, entered the Collis P. Huntington Memorial Hospital in June, 1927. He complained chiefly of fatigue, bloating and pain in his legs. An enlarged spleen could be felt and there was bilateral inguinal lymph-node enlargement. His blood showed a moderate elevation of white cell count with 6.5 per cent plasma cells. There were also cells of the lymphocyte series which were difficult to classify. He was given Roentgen ray treatments over the spleen with complete disappearance of symptoms and a marked lessening of the size of the spleen. A year later symptoms returned and the spleen became larger. Roentgen ray treatments again improved the condition. The blood continued to

* We are indebted to Dr. Francis Nash for his kind permission to publish the report of this case.

show many typical plasma cells, as well as atypical lymphocytes. Eight months later his blood seemed normal but the spleen remained enlarged and lymph adenopathy was generalized. Two biopsies on lymph nodes from the groin, however, failed to show any pathology. The exact nature of this patient's condition must, therefore, remain obscure. That it is akin to the other cases would be indicated by the persistent presence of plasma cells in the blood stream.

Discussion. In Case I a plasmocytoma of the tonsil was removed eight years before generalized bone involvement could be detected. For fully seven years the patient showed no signs or symptoms which could be attributed to bone lesions, yet during all this time the process was spreading through the lymphoid system as was proved by successive lymph node involvement, and eventually bone lesions characteristic in all ways of multiple myeloma made their appearance.

The histology of the several lymph nodes removed and of the bone tumor at autopsy was identical. Each showed a plasmocytoma. There would seem to be no doubt but that the plasma-cell tumor arose in the tonsil, spread through the lymphatic system, and finally reached the marrow. We have been unable to find in the literature any analogous case.

In Case II it is difficult to say positively whether the lesions appeared first in the bones or in the lymph nodes. That an enlargement of a lymph node first brought the patient to the hospital is apparent. Symptoms compatible with classical multiple myeloma—in this case, pains in the hip—had been present for some time, and while Roentgen rays did not demonstrate any lesions until later, it is quite possible, and in fact, likely, that they were present when the patient first presented himself at the clinic. Our experience with both malignant lymphoma and metastatic carcinoma would lead us to believe that bone lesions may exist for some time before they are detectable by Roentgen ray. The initial tumor in this case was a plasmocytoma. Cervical lymph nodes became involved, a retroperitoneal mass of considerable size developed, and the bone changes, though at first considered more characteristic of metastatic carcinoma, later were judged consistent with multiple myeloma.

While it was impossible to obtain a specimen from a bone for pathologic examination, the absence of any evidence of carcinoma, together with the presence of a rapidly growing extra-osseous plasmocytoma makes it reasonable certain that the case was one of multiple myeloma with widespread extra-osseous involvement.

In Case III the tumor was again a plasmocytoma but no metastases were observed either in the bones or elsewhere. The tumor would seem, therefore, to have been relatively benign. It should be remembered, however, that eight years elapsed in the first case before osseous involvement was detected.

Case IV presented a plasmocytoma possibly arising from and

involving the alveolar process. The histology of the tumor was identical with that of the other cases. Radiation and excision caused a temporary cure but the patient died several months later, presumably from cerebral hemorrhage. No evidence was at hand that there was involvement of other bones.

Case V is more difficult to classify. No bone lesions have been demonstrated and biopsy showed a normal lymph node. The blood, however, has shown from time to time relatively large numbers of typical plasma cells. As noted above, Piney (1924) describes a case of plasma-cell leukemia. His patient, a man aged forty-eight years, complained of pain in the legs and lumbar spine. There was an enlarged spleen and the blood showed an elevated white blood cell count with from 14 to 41 per cent plasma cells. Autopsy showed infiltration of the ribs, femurs and spine. The spleen and liver showed marked infiltration with plasma cells. Piney regarded the case as one of leukemia, in which plasma cells took the place of the more usual lymphocytes, rather than multiple myeloma because the tumor in the bones was diffuse and because there was no Bence-Jones protein in the urine. In our series, Case V most nearly approaches Piney's case and is included for this reason.

Thus plasmocytomata may arise in lymphoid structures and subsequently involve bones, arise in bones and extend to lymph nodes, arise in and remain in lymph nodes without further extension, and arise in bone without further spread. Furthermore, there occurs plasma-cell leukemia with or without extensive participation of the bone marrow.

It is often difficult to say from pathologic evidence when one clinical entity ends and another begins. Additional cases are likely to bring together under one head clinical pictures previously widely separated. Specificity in disease, as in other biologic classifications, must depend in the last analysis upon the presence or absence of imperceptible gradations between apparently different clinical entities.

From the cases reviewed here and from the cases in the literature, it would seem that there is no very sharp line of demarcation between localized, benign plasmocytomata on the one hand, and the malignant, fatal multiple myelomata on the other. No clear distinction can be seen again between the nodular, circumscribed form and the diffuse form. We have recently seen a case presenting both the nodular and the diffuse type of involvement. Both have been seen in one patient in our series (that of Dr. Shortell). The bones may be involved first and internal organs later, or the process may be reversed. In a given case one cannot predict what course the plasmocytoma will take.

Plasma cells are generally admitted to arise from the small and medium-sized lymphocytes through individual differentiation which is not accompanied by mitosis and is caused presumably by peculiar

unknown chemical stimuli (Maximow, 1928), (Pappenheim, 1907. 2). Furthermore, both plasma cells and lymphocytes are known to be normal, though perhaps rare, constituents of bone marrow (Naegeli, 1908), (Vogt, 1912), (Maximow, 1928), (Martin, Dechaume and Levrat, 1928). It is readily apparent, therefore, how plasmocytomata may arise in almost any situation in the body and according to circumstances give rise to tumors of variable gross behavior and consequently of varying degrees of malignancy. Fundamentally the process is the same, but the clinical picture and the gross pathology may vary within wide limits.

A similar assortment of pathologic processes has been grouped under the general heading of malignant lymphoma.

There occur localized lymphocytomata, some relatively benign, others generalized processes involving many lymph nodes, lymphosarcomata invading surrounding tissues, and lymphatic leukemia. Bone involvement is not at all rare, even in the absence of leukemia. Symptoms referable to bone lesions may be the first that attract the patient's attention, as in one of our cases.

Conclusion. We believe that multiple myelomata of the plasma-cell type (at least), should be classed among the malignant lymphomata. The type cell belongs beyond question to the lymphoid series, and the clinical picture finds analogies throughout its course in the pathologic and symptomatic picture of the lymphomata. That the disease in its classical form is largely limited to the bones does not militate against such a view when one considers the marked variation of the disease picture and the gradual manner in which the cases blend into each other.

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CALCIUM AND PARATHYROID THERAPY IN CHRONIC ULCERATIVE COLITIS.

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This report consists of an experimental and a clinical study of the nonspecific form of chronic ulcerative colitis. The experimental studies include the determination of the diffusibility of calcium in 6 patients with mucous colitis, 2 with spastic colon, and 7 with chronic ulcerative colitis. The clinical study consists of the observation of 13 patients with chronic ulcerative colitis, with particular reference to the effects of calcium and parathyroid therapy.

Experimental Investigation. The essential rôle played by inorganic elements in the maintenance of normal cellular function has long been recognized by physiologists. The life and functional integrity of the cell are dependent upon the interchange of material between the interior and exterior of the cell; glucose and amino-acids must pass in and the products of metabolism must pass out. This interchange depends upon the permeability of the cell membrane, which, in the resting state, is impermeable to colloids and to most crystalloids, allowing the free passage of certain substances such as urea, alcohol, glycerol and ammonium salts. Obviously, such a state is incompatible with life. Certain functional states of the cell are known to be accompanied by alterations in permeability. As stated by Bayliss,[1] "A consideration of the evidence forces upon us the conclusion that the cell membrane is sometimes permeable to crystalloids, sometimes not. This behavior is in relation to functional changes in the cell or is dependent on the action of definite substances." It is well recognized and readily demonstrable that normal permeability is dependent to a considerable extent upon the

presence of a normal balance between the inorganic ions in the fluid bathing the cell. Calcium diminishes cell permeability; in fact, Loeb[2] attributes the general inhibiting action of calcium to this property, which is affected by relatively minute alterations in calcium concentration.

It can be readily demonstrated experimentally that alterations in cell permeability can exist for prolonged periods of time with no permanent structural damage, the normal state being restored upon correction of the abnormality of permeability. It seems evident, therefore, that clinical manifestations of disordered cell function may result from such abnormalities of cell permeability, which may be dependent upon deviations from the normal balance of electrolytes in the blood and tissues. This condition, if persistent and progressive, eventuates in demonstrable structural damage. Viewed in this light, the metabolic, nutritional and general physiologic importance of the inorganic elements, particularly sodium, potassium and calcium, seems evident.

The existing limitations of experimental and analytic methods and the wide gaps in our knowledge of the details of the metabolism of inorganic elements have precluded the possibility of a thorough study of the balance of inorganic ions in disease states. The equilibrium between these elements, being so essential to the well-being and functional normality of the organism, is maintained much more delicately than is the case with organic substances and their derivatives. It is extremely difficult clinically and even experimentally to investigate directly the conditions present in the tissues. We must be content with the study of the available body fluids, particularly the blood, and attempt to interpret from such a study the conditions in the various tissues. However, in the case of inorganic elements particularly, the difficulty arises that by virtue of an elaborate equilibrating mechanism, local tissue variations may not be reflected in the circulating blood. This has been beautifully demonstrated by Rous and Drury,[3] who showed that local tissue acidosis can exist, due to functional ischemia, with no corresponding alteration in blood reaction; in fact, in some instances the blood becomes more alkaline while the tissue acidosis is developing. In view of such findings, the difficulties inherent in the clinical investigation of inorganic ion balance are apparent.

Practically all studies of the condition of calcium metabolism and balance have concerned themselves with the determination of the intake and output of calcium and its concentration in the blood. The important question of the partition of calcium into its diffusible and nondiffusible fractions has been almost completely ignored, despite the fact that only by the estimation of these fractions can the distribution of calcium in the tissues be determined. The recent studies of Peters and Eiserson[4] and of Snell[5] apparently indicate that the determination of diffusible calcium is of no practical clin-

ical significance. However, the fact is lost sight of that in certain disease conditions there is an alteration in cellular and capillary permeability, and that under such circumstances, while the relative proportions of diffusible and nondiffusible calcium in the blood serum may be normal, the amount of calcium which has diffused into the tissue fluids may be altered. Thus "diffusible" and "diffused" calcium, although identical under conditions of normal permeability, may not always be so in disease. The former may be measured by dialysis and ultrafiltration, the latter only by the determination of the calcium content of some body fluid representative of the tissue fluid. The cerebrospinal fluid has been utilized for this purpose. Following this procedure, one of us (A. C.), in previous studies,[6,7] found a distinct increase in the ratio of "diffused" to "nondiffused" calcium in a group of conditions believed to be associated with alteration in capillary and cellular permeability, such as bronchial asthma, vasomotor rhinitis, mucous colitis and some cases of pulmonary tuberculosis. In the great majority of these the total serum calcium was within normal limits.

Calcium Studies in Colitis. In the present study, simultaneous determinations of the calcium content of the blood serum and cerebrospinal fluid were made in 6 patients with mucous colitis, 2 with spastic colon and 7 with chronic, nonspecific, ulcerative colitis. The determinations were made by the Clark-Collip modification of the Kramer-Tisdall procedure.[8] The pertinent data are presented in Table I. The cerebrospinal calcium is termed "diffused" calcium, the difference between it and the serum calcium being termed "nondiffused" calcium.

TABLE I.—CALCIUM PARTITION IN 6 PATIENTS WITH MUCOUS COLITIS, 7 WITH CHRONIC ULCERATIVE COLITIS AND 2 WITH COLONIC SPASM.

Condition.	Case.	Serum Ca.*	Diff.*	Nondiff.*	D/ND.*
Mucous colitis	1	11.00	6.00	5.00	120
" "	2	10.32	5.71	4.61	121
" "	3	9.84	5.62	4.22	156
" "	4	10.24	5.92	4.28	138
" "	5	9.96	5.54	4.42	125
" "	6	9.21	5.70	3.51	162
Ulcerative colitis	7	8.71	6.15	2.56	240
" "	8	9.64	5.61	4.03	139
" "	9	9.84	5.62	4.22	156
" "	10	11.25	5.50	5.75	96
" "	11	10.75	5.75	5.00	115
" "	12	11.00	5.00	6.00	83
" "	13	8.80	4.52	4.28	105
Spastic colon	14	9.34	5.66	3.68	153
" "	15	9.61	5.43	4.18	129

* Calcium expressed in mg. per 100 cc. "Diff." refers to diffused calcium. "Nondiff." refers to nondiffused calcium. "D/ND" is the ratio of diffused to nondiffused calcium expressed as percentage.

SPASTIC COLON. In the 2 patients with spastic colon the serum calcium was 9.34 and 9.61 mg. per 100 cc., the cerebrospinal fluid

calcium was 5.66 and 5.43 mg. per 100 cc. The nondiffused calcium, represented by the difference between the serum and cerebrospinal fluid values was 3.68 and 4.18 mg. The ratio of diffused to nondiffused calcium was 153 and 129 per cent respectively.

Mucous Colitis. In the 6 patients with mucous colitis, the serum calcium varied from 9.21 to 11 mg. per 100 cc.; the diffused calcium ranged from 5.62 to 6 mg., the nondiffused calcium from 3.51 to 5 mg. The ratio of diffused to nondiffused calcium ranged between 120 and 162 per cent.

Ulcerative Colitis. In the 7 patients in this group the serum calcium ranged from 8.71 to 11.25 mg. per 100 cc., the diffused calcium from 4.52 to 6.15 mg. and the nondiffused calcium from 2.56 to 6 mg. The ratio of diffused to nondiffused calcium varied between 83 and 240 per cent.

Discussion. In a previous investigation,[6] the normal partition of calcium was found to be as follows: Serum calcium 9 to 11 mg., diffusible calcium 4.5 to 5.5 mg. and nondiffusible calcium 4.7 to 5.75 mg. per 100 cc., the ratio of the diffusible to the nondiffusible fraction being 82 to 115 per cent. In a subsequent study,[7] it was noted that in practically all patients with some manifestation of allergy or of autonomic imbalance such as bronchial asthma, vasomotor rhinitis, angioneurotic edema and mucous colitis, the diffusibility of calcium was increased (Table II). This was evidenced by an increase in the ratio of diffused to nondiffused calcium. Since the cerebrospinal fluid calcium was determined as representing the diffusible fraction of serum calcium, it could not be decided, under the conditions of the investigation, whether the increased diffusibility is due primarily to a disturbance in the partition of calcium in the blood or to an alteration in capillary and cellular permeability. However, Brown and Ramsdell,[9] utilizing the artificial membrane method, found a marked increase in the diffusibility of calcium in experimental anaphylaxis in the guinea pig, suggesting that this phenomenon may be of primary significance, particularly in allergic conditions.

Table II.—A Comparison of the Diffusibility of Calcium in Allergic, Vasomotor and Autonomic Disorders and in Mucous Colitis and Ulcerative Colitis.

Condition.	Cases.	Serum Ca.*	Diff.*	Nondiff.*	D/ND.*
Normal	68	9–11	4.5–5.5	4.7–5.75	82–115
Asthma	25	7.0–12.67	4.39–6.33	1.5–7.5	68.9–400
Vasomotor rhinitis	2	10.55–10.7	5.75–6.1	4.45–5.0	115–137
Angioneurotic edema	1	8.2	5.5	2.7	203
Spastic colon	2	9.34–9.61	5.43–5.66	3.68–4.18	129–153
Mucous colitis	6	9.21–11.00	5.62–6.00	3.51–5.00	120–162
Ulcerative colitis	7	8.71–11.25	4.52–6.15	2.56–6.00	83–240

* Calcium expressed in mg. per 100 cc. "Diff." refers to diffused calcium. "Nondiff." refers to nondiffused calcium. "D/ND" is the ratio of diffused to nondiffused calcium expressed as percentage.

It appears significant that the calcium diffusibility ratio was found to be increased in all of the patients with spastic colon and mucous colitis. This finding is of especial interest in view of the associated manifestations of autonomic imbalance which are usually present in these disorders. The frequency of such manifestations has recently been emphasized by Bockus, Bank and Wilkinson.[10] The evidence of a disturbance of calcium partition in these conditions serves to emphasize the fundamental relationship between autonomic balance, capillary permeability and electrolyte equilibrium. Parasympathicotonia (vagotonia), as shown by the work of Petersen,[11] is associated with capillary dilatation, increased permeability, and calcium deficiency in the tissues; sympathicotonia is accompanied by decreased permeability and a relative calcium excess. It is of interest to note that in every case but one (Case XV), the increase in the diffusibility ratio was associated with an increase in the amount of diffused calcium, thus obviating the possibility that it was dependent upon a primary decrease in the nondiffusible fraction resulting from a diminution in serum proteins.

Of the group of 7 patients with chronic ulcerative colitis, 3 showed an increase in the calcium diffusibility ratio comparable to that observed in the group with mucous colitis; in 4 cases the ratio was within normal limits. In the 3 cases with increased ratios the actual amount of diffused calcium was increased, despite the fact that in one instance (Case VII) the serum calcium was slightly subnormal. What is the significance of this variation in calcium partition? Unfortunately, the patients upon whom the calcium determinations were made are not included in the group studied from the standpoint of calcium therapy. We cannot, therefore, correlate the calcium findings with the therapeutic response in each case. However, these findings strengthen the belief, mentioned later, that in a certain proportion of cases of ulcerative colitis, mucous colitis serves as an etiologic basis.

The concept of the relationship of disturbances in the equilibrium of the vegetative nervous system to gastrointestinal ulcerations is an old one. There is a large amount of experimental data in the literature of this subject, particularly with regard to the origin of gastric and duodenal ulcer. The consensus of opinion of those who believe in this etiologic relationship appears to be that ulceration results from a disturbance of autonomic balance in the direction of vagotonia, probably operating through its consequent effect upon vasomotor tone. It is not inconceivable that serious nutritional disturbance in predisposed areas may result from the combined factors of autonomic and vasomotor imbalance, altered capillary and cell permeability, and a disturbance in calcium distribution.

Effects of Calcium Therapy. The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the effect of calcium on one or more of four possibly existing conditions: (1) Parathyroid

dysfunction; (2) nutritional change in the tissues, with or without a disturbance of calcium partition; (3) spastic colon; (4) hemorrhage.

(1) Parathyroid Dysfunction. There is no evidence of any abnormality of parathyroid function in ulcerative colitis. The pathologic chemistry of hypoparathyroidism and hyperparathyroidism has been quite definitely established, the findings in both conditions being rather characteristic. Grove and Vines[12] raised the question of the possibility of parathyroid deficiency in certain chronic ulcerative conditions on the basis of a disturbance in the proportion of ionized calcium in the blood and the beneficial results of parathyroid therapy. However, there is no satisfactory method for the determination of ionized calcium and the findings recorded by these investigators do not conform to those considered characteristic of parathyroid deficiency.

(2) Nutritional Change in Tissues. There is, unquestionably, a local disturbance of nutrition in ulcerative colitis. Whether or not the fundamental fault lies in the tissues is, of course, a controversial point. The evidence in favor of the belief in the etiologic agency of an alteration in calcium distribution, abnormal capillary and cell permeability, autonomic imbalance and altered vasomotor tone has been reviewed above.

Grove and Vines[12] noted marked improvement in a variety of chronic ulcerative conditions following the administration of calcium salts and parathyroid extract. They believe that some abnormality of calcium ionization is concerned with the maintenance of the chronicity of such lesions and that such therapy should not be considered as a specific cure but as a rational method of stimulating the cellular elements to exercise their proper defensive mechanism. The most consistently beneficial results of calcium therapy in intestinal ulcerations has been noted in intestinal tuberculosis. Brown and Sampson[13] state that calcium is probably the best remedy we possess today for the relief of this condition. Varied explanations are given for its action. According to Starkenstein,[14] calcium inhibits the inflammatory process and augments the functional capacity of the whole organism for reaction. Mandl[15] and Fishberg[16] believe that the effect is exerted through the vegetative nervous system, decreasing peristalsis. Another way in which calcium may favorably influence the healing of the ulcerations is through its anti-edemic action which, in spite of some contradictory evidence, is a well-established physiologic fact.

(3) Spastic Colon. Colonic spasm, which is almost invariably present in ulcerative colitis, is an evidence of increased vagus excitability or excitation. Muscular spasm in the region of the ulcerations must inevitably interfere with healing, and relief of this spasm plays an important part in the successful treatment of the condition. The relationship between autonomic balance and electrolyte balance has been conclusively demonstrated by many investi-

gators, among the more recent of whom are Zondek,[17] Kolm and Pick,[18] Andrus and Carter[19] and Loewi.[20] The subject has been extensively reviewed by Sollmann.[21] As a result of these investigations it is now recognized that vagotonia is associated with a relative decrease in tissue calcium ions in proportion to potassium and sodium ions. Sympathicotonia is associated with an imbalance in the opposite direction. Since a normal proportion of calcium ions appears to be necessary for the normal effect of adrenalin on the sympathetic nerve endings, a diminution in their concentration results in a preponderance of the opposing vagal impulses manifested in the intestine by spasm. The relaxant effect of calcium appears to be one of the most important factors in the production of symptomatic relief and anatomic improvement in ulcerative colitis.

(4) HEMORRHAGE. Bleeding should be considered not only as a result of the ulcerative process but also as a factor which tends to prevent healing and to maintain chronicity of the lesion. This hemorrhagic tendency is not due to any inherent disturbance of the mechanism of coagulation nor entirely to vascular erosion; it depends in part upon some nutritional error in the tissues which, in view of the reported findings, probably consists of increased capillary permeability and altered calcium distribution. In a previous study[22] it was observed that parathyroid extract, by causing a sharp increase in the available calcium of blood and tissues, has a definitely beneficial effect upon bleeding of a slow, oozing nature. In the majority of patients with ulcerative colitis, cessation of bleeding was one of the earliest and most constant features of the response to calcium and parathyroid therapy. This, undoubtedly, has a favorable influence upon the healing of the ulcers.

Clinical Investigation. The effects of treatment in a series of 13 patients are presented. Ten of these have been under observation over a period of one to two and a half years. Bacteriologic studies of material obtained from the bowel wall through the proctoscope failed to disclose the presence of amœba or specific bacterial organisms, including the organism reported by Bargen.[23,24] Various strains of streptococci were found in either pure or mixed culture. The age incidence varied from twenty to fifty-eight years. The duration of symptoms was from one month to twelve years. Six patients had been previously treated with colonic irrigations. In 2 of these an appendicostomy had been performed, following which 1 remained symptom-free for four months, the other for three years. The period of calcium and parathyroid therapy varied from four to twelve weeks. Three patients did not continue treatment after four weeks and have not been traced. The remaining 10 were seen at intervals and have been examined during the past two months.

Most of these patients have been observed and treated through the courtesy of Dr. J. Hall Allen, Chief of the Proctologic Service, Jefferson Hospital.

PLAN OF TREATMENT. The form of treatment includes: (1) A cellulose-free, nonirritating diet; (2) belladonna and kaolin; (3) calcium salts, ammonium chlorid and parathyroid extract administered as follows:

Calcium. Calcium chlorid, calcium lactate and calcium gluconate* were the salts used. The majority of the patients received either the lactate or the gluconate, the latter being perhaps more easily tolerated. Any form of calcium therapy, to be effective, must be administered with some understanding of certain facts concerning the absorption of calcium from the intestine. Without going into detail, it is necessary only to recall the fact that calcium is absorbed best when the intestinal alkalinity is lowest. Therefore, to secure maximum absorption, it must be administered at times when upper intestinal digestive activity is at a minimum, that is, a short time before meals. This has been well demonstrated by Roe and Kahn[25] who showed that even the administration of 250 cc. of milk with calcium reduces its absorption by about 60 per cent. They obtained an average rise of 80 per cent in serum calcium after the oral administration of 5 gm. of calcium lactate in aqueous solution in fasting subjects. Calcium lactate (powder), 30 gr., or calcium gluconate, 60 gr., was, therefore, administered orally three or four times daily, three and a half to four hours after meals. The patients are cautioned to avoid eating between meals. By following this routine, in the majority of instances one may be fairly certain of securing an adequate amount of absorption.

Ammonium Chlorid. The mere fact of adequate calcium absorption does not necessarily indicate adequate utilization. It has frequently been demonstrated, experimentally and clinically, that ammonium chlorid, by increasing the hydrogen-ion concentration of the tissues causes an increase in the availability or utilization of the tissue calcium. Ammonium chlorid is well tolerated by the majority of patients. It is administered in doses of 20 to 30 gr. in capsule or powder form, together with the calcium salt.

Parathyroid Extract. Collip states[26] that the function of the parathyroid hormone, in the normal animal, "appears to be that of a regulator of calcium metabolism, and its action is primarily as a calcium mobilizer." Our investigations into the action of parathyroid extract[27,28,29] suggest that its injection results in an increase in the availability and utilization of calcium, as well as in a tendency toward the restoration of a normal ratio of diffusible to nondiffusible calcium.

Parathyroid extract (Para-thor-mone) is injected intramuscularly, the average adult dose being 20 to 30 units, varying with body weight. The injections are repeated at intervals of forty-eight to seventy-two hours, depending upon the severity of the symptoms.

* The preparation used was calcium-Sandoz, supplied through the courtesy of The Sandoz Chemical Company.

TABLE III.—SUMMARY OF CASES TREATED.

Patient.	Age.	Duration of symptoms.	Previous treatment.	Special features.	Duration of calcium treatment.	Period of observation.	Present appearance of mucosa.	Condition since treatment.
J. E. B.	35	8 mos.	Irrigations 3 mos.	.....	6 weeks	30 mos.	Slight congestion	Well.
C. T.	48	8 mos.	Dietetic; sedatives	30 pounds loss in weight and nervous phenomena	8 weeks	24 mos.	Normal	Occasional mucus.
B. O. G.	26	10 yrs.	Appendicostomy in fifth year; irrigations	Frequent remissions, longest 4 months	8 weeks	22 mos.	Reddened and thickened	Symptom-free 14 months.
M. A.	41	4 yrs.	Sedative drugs	Lower rectum slow in healing	4 weeks; after 2 mos., 8 weeks	24 mos.	Normal 4 mos. after treatment ended	Tendency toward constipation.
E. d'A.	30	1 yr.	Irrigations; diet; sedatives	Abdominal pain marked	6 weeks	30 mos.	Slight congestion	Occasional mucus in stool.
S. B.	27	2 yrs.	Dietetic	Associated with nervous symptoms	4 weeks	24 mos.	Glazed, pale	Acute attack for 1 week a year later.
J. H.	54	4 mos.	None	.....	7 weeks	12 mos.	Normal	Return of symptoms after 8 mos.
F. S.	45	4 yrs.	Irrigations	.....	8 weeks	26 mos.	Normal	Occasional mucus.
H. S.	45	12 yrs.	Appendicostomy; normal saline irrigations	Symptom-free 3 yrs. after operation	4 weeks, then discontinued	Not traced	No bleeding ulcers; not entirely healed	
F. E.	20	7 mos.	None	.....	6 weeks	Not traced	Slightly edematous and granular.	
I. K.	58	3–4 wks.	Rectal instillations	.....	7 weeks	13 mos.	Normal	Well.
R. S.	25	12 yrs.	Dietetic	Remissions 4 mos. yearly almost	3 mos.	10 mos.	No improvement	Bleeding only occasionally; frequency of stool persists.
J. S.	30	3 yrs.	None	.....	1 mo.; discontinued	1 mo.; did not continue	No improvement.	

Case Reports. CASE I.—J. E. B., aged thirty-five years, for eight months there were frequent evacuations of blood and mucus, especially in the morning, moderate abdominal pain and nervousness. The mucosa of the bowel was markedly congested and edematous, with scattered small ulcerations in the rectum and lower sigmoid. Response to treatment with diet and irrigations was slow. After three months symptoms were relieved but the mucosa showed little change. Calcium and parathormone were administered in addition to the other treatment. After three weeks the bleeding had ceased and the ulcers showed evidence of healing. In six weeks all ulcerations were healed and only slight congestion of the mucosa remained. He has remained well since September, 1927.

CASE II.—Mrs. C. T., aged forty-eight years, attacks of frequent soft bowel movements containing much mucus and lasting two to three days had occurred every few weeks for eight years. These attacks were usually associated with disturbed mental states, as excitement or fright. For the last eight months there had been a continuous frequency of movements, ten to fifteen a day, with much blood and mucus. A loss of 30 pounds in weight had occurred. The first examination, difficult because of the profuse bleeding, showed a soft, boggy mucosa with numerous pinhead-sized ulcerations, as far as the sigmoidoscope could be passed. Response to calcium-parathyroid therapy was surprisingly rapid. In ten days she felt better, the bleeding was slight and the number of bowel movements was greatly reduced. At the end of a month, there was a gain in weight of 5 pounds, with one or two well-formed stools daily without blood or mucus. Examination two months after treatment was instituted showed a practically normal mucosa, without evidence of the previous ulcerations. During the past two years she has been well except for the occasional passage of mucus.

CASE III.—B. O. Q., aged twenty-eight years, following an attack of grippe in 1918, began to pass clots of blood. This was followed in a few weeks by frequent bowel movements, eight to fifteen daily, with blood and mucus. He was treated with irrigations and remained symptom-free for five months when the previous symptoms returned. An almost regular cycle of remissions and exacerbations now followed, with attacks lasting about six months and symptom-free remissions about four months. In 1923 an appendicostomy was performed, following which he was well for the longest period—six months. The opening was kept patent and when fresh attacks occurred, it was used as a means of irrigation. Recovery required less time by this method of irrigation than by the former method. When examined in May, 1928, the mucosa of the bowel was granular, with scattered ulcers and many small pitted scars of healed areas. Calcium and parathyroid were given, in addition to the irrigations. This attack was of shorter duration than any previously—about four months. Gaining 15 pounds, he weighed more than ever before. He remained well until September, 1929, fourteen months later, when symptoms returned. This time irrigations were not used and the attack was the shortest in his experience—two months. No symptoms have occurred since. The prompt recovery from symptoms without the use of irrigations has led the patient to desire closure of the appendicostomy wound.

CASE IV.—Mrs. M. S., aged forty-one years, was first examined in July, 1927. For four years she had been passing blood with nearly all bowel movements, which were usually constipated. The preceding fall there began to occur frequent watery and bloody stools associated with attacks of abdominal pain. Belladonna and bismuth, with rectal instillations, relieved the more distressing symptoms, but bleeding and semiliquid stools

persisted. Calcium and parathyroid were administered for one month and the bleeding was slight and occasional. Treatment was discontinued for two months but then renewed for eight weeks, after which time examination showed the upper rectum and sigmoid practically normal, but the lower 2 inches still boggy and bleeding to touch. Three months later this had resumed a normal appearance. She has remained well since March, 1928, but requires mineral oil regularly to avoid constipation.

Case V.—E. d'A., aged thirty years, for a year, excepting two months during the winter, had frequent bowel movements containing a small amount of blood and mucus, and associated with severe abdominal pain, loss of weight and marked mental depression. The mucosa was deeply congested, with a glazed surface and scattered irregular ulcerations. With modified diet and irrigations for two months, the pain and frequency of movements were reduced, but the bleeding persisted. Calcium and parathyroid were given for six weeks, after which time period the bleeding ceased and the ulcers healed, leaving tiny pitted scars. Except for the occasional passage of mucus he has remained well since August, 1927.

Case VI.—Mrs. S. B., aged twenty-seven years, for two years, there were eight to ten bowel movements daily, with much mucus and flatus, some blood and abdominal cramps, relieved by expelling gas. Mental strain or excitement brought an increased number of evacuations. During the summer months her symptoms were less severe although blood and mucus were always present. After three weeks of calcium and parathyroid therapy and under proper dietetic régime, the bleeding stopped and there were one or two well-formed stools daily. As long as a nonirritating diet was followed the patient remained symptom-free since February, 1928. After an occasional dietetic debauch she suffers from abdominal pain, relieved by passing large amounts of mucus. In December, 1929, there was an acute exacerbation lasting one week, with frequent stools containing much blood. This followed an acute respiratory infection, but subsided quickly and she has been well since.

Case VII.—J. H., aged fifty-four years, was admitted March, 1929, to the surgical service of Dr. Da Costa with a diagnosis of possible carcinoma of the sigmoid after Roentgen ray examination with barium enema. Since the previous December he had complained of pain in the left iliac region, bearing-down pain on defecation, blood and mucus in the stools, five or six times daily. Sigmoidoscopic examination disclosed a mucopurulent secretion, mixed with blood, exuding from many small ulcers in the rectum and sigmoid. Two months later there was only moderate congestion of the mucosa with spasm of the bowel wall. A subsequent Roentgen ray examination failed to disclose the previous filling defect in the sigmoid. Calcium and parathyroid had been administered for seven weeks.

Case VIII.—F. S., aged forty-five years, was admitted to the service of Dr. Hare, September, 1927, with frequent evacuations of blood and mucus and lower abdominal pain. Since the onset four years ago periods of quiet alternated with recurrence of symptoms at almost regular intervals, each period of three to four months' duration. Irrigations relieved the pain, reduced the frequency of bowel movements but did not stop the bleeding. Calcium and parathyroid were given for four weeks, then calcium lactate alone for a similar period. Since December, 1927, he has been without recurrence of bleeding, but passes mucus occasionally. Present examination shows a moderately anemic mucosa with a few pocklike scars.

CASE IX.—H. S., aged forty-five years, was seen in January, 1929, with a history that marked constipation with the passage of blood, and a mucopurulent discharge from the bowel began twelve years before. An appendicostomy had been performed, following which he was symptom-free for three years, and during this period the wound had closed. Since then rectal bleeding and mucoid discharge had been almost constantly present. On examination the lumen of the bowel was markedly narrowed, blood oozed from the rectal wall and a purulent exudate filled the sigmoid. A few jagged ulcers were present. Normal saline irrigations were given locally in addition to calcium and parathyroid. At the end of a month bleeding had ceased and the mucosa had lost its hemorrhagic appearance, but the ulcers had not entirely healed. At this time the patient discontinued treatment at the outpatient department and has not been seen since.

CASE X.—F. E., aged twenty years, the only colored patient in this series, was seen in May, 1928. For seven months he had frequent bloody bowel movements with lower abdominal pain. The mucosa was extremely congested and edematous, showing a few irregular ulcers, varying in size up to 1 cm. Cultures made from the bowel wall predominated in hemolytic streptococci. After six weeks of the present plan of treatment bleeding had ceased, and the number of bowel movements was reduced to two soft stools daily. The mucosa was still edematous and granular, with the ulcers partially healed. He discontinued treatment and we have been unable to trace him since.

CASE XI.—I. K., aged fifty-eight years, in February, 1929, suddenly developed an acute colitis with ten to fifteen watery stools daily, containing a slight amount of blood. His history was negative except for typhoid fever thirty years before, at which time he passed blood by bowel. At examination there were many minute ulcerations in the mucosa. Rectal instillations were given, in addition to calcium and parathyroid, but there was little change for two weeks. After this period he rapidly improved and three weeks later the symptoms had subsided. At this time there were no ulcerations, but some edema and congestion of the mucosa. In another month the bowel presented a practically normal appearance and he has remained well since.

CASE XII.—R. S. aged twenty-five years; the onset of occasional frequency of soft, mushy stools with slight bleeding occurred twelve years before. There were periodic remissions, but the longest period of freedom from symptoms had been four months. Periods of activity lasted from eight to fourteen months. Calcium and parathyroid were administered for three months, together with a proper diet and sedative drugs, but no appreciable change in symptoms resulted. The bleeding would temporarily decrease, but always recurred. Other methods of treatment, autogenous vaccine and irrigations, have been used subsequently without success.

CASE XIII.—J. S., aged thirty years, had for three years several semiliquid, bloody stools daily. Occasionally, for a few days at a time, his symptoms would subside. Calcium and parathyroid were given for one month, but at the end of this time there was no appreciable change in symptoms or in the appearance of the bowel. The patient was apparently discouraged, discontinued further treatment, and has not been seen since.

Discussion. Of the 13 patients, only 10 have been observed over a sufficient period of time to permit of definite conclusions. Of the remaining 3, 2 improved symptomatically to a degree which led

them to discontinue further treatment. It is, therefore, in a group of 10 patients that the effects of calcium and parathyroid will be reviewed.

Nine became symptomatically well in from four to twelve weeks. Of these, 7 have remained entirely well for two years or more, while in 2 exacerbations occurred. The tendency to remissions is a well-known feature of the disease and accounts for the difficulty in determining when complete recovery takes place. The periods of inactivity are usually of several months' duration although some observers believe they may extend over many years. Whether the disease is actually latent for a long period of time, or whether it recurs as a new attack distinct from the earlier, seems controversial. According to Crohn and Rosenberg,[30] the remission stage of colitis represents only a temporary subsidence of evident phenomena with a latent persistence of low-grade infection. They emphasize the fact that before a patient be considered entirely well there must be not only freedom from all subjective and objective symptoms, but also a normal appearance of the mucous membrane on sigmoidoscopic examination. Similar criteria have been applied in the present study.

In 1 of the 2 patients in whom symptoms recurred, the bowel did not resume a normal appearance but remained reddened and thickened. Previously, in the course of his disease, remissions were frequent, but never for more than six months, usually less. He was treated with irrigations through an appendicostomy wound. Following the use of calcium and parathyroid he remained well for fourteen months. Symptoms returned but again subsided after the calcium was renewed. He has been symptom-free for another six months, although the bowel still shows evidence of chronic inflammation. In 1 other patient, a return of symptoms occurred after eight months, in spite of an apparently complete recovery, clinically and on sigmoidoscopic examination. A renewal of calcium therapy again brought relief. In 8 patients the mucous membrane of the lower bowel returned to a practically normal state after all symptoms had subsided and has remained so. Occasionally, minute pocklike scars have persisted as the only evidence of the previous ulcerations.

Certain facts have been observed in the therapeutic response to calcium. The beneficial effect of parathyroid extract upon bleeding of a slow, oozing nature has been previously mentioned. In all patients cessation of bleeding was the earliest and most constant feature. Whether healing of an ulcer precedes or follows the interruption of bleeding is a controversial point. However, sigmoidoscopic examination has repeatedly disclosed unhealed ulcers without evidence of bleeding. The influence of calcium and parathyroid upon hemorrhage is regarded as an important factor in accounting for their beneficial effect upon the lesions of ulcerative colitis.

Another important result of calcium therapy has been its relaxant effect upon colonic spasm. The physiologic principles accounting for this effect have been mentioned. The pain produced by spasm, as well as its inhibitory effect upon healing, are recognized, and an attempt is always made to reduce this excessive muscle tonus. In 3 patients who had been previously treated without marked relief of symptoms, this relaxant effect of calcium, as well as its influence upon bleeding, were demonstrated. Belladonna had been administered to the limit of tolerance and irrigations were used regularly, with only partial symptomatic relief. After ten days of calcium and parathyroid treatment there was a noteworthy reduction in the quantity of blood passed and definite relief from pain, which gradually ceased. The persistence of pain for three months, not relieved by belladonna and local treatment, and the change induced by calcium in about ten days, serves to emphasize this important relaxant effect.

In the experimental studies it was found that in a certain proportion of patients with ulcerative colitis, the alteration in the calcium partition was similar to that found in all the patients with mucous colitis. This suggested a distinct relationship between the two conditions. This possibility is at variance with the generally expressed views which hold that mucous and ulcerative colitis are two distinct entities. An occasional suggestion to the contrary, however, has been noted. Mallory[31] regards spastic constipation, mucous colitis and chronic ulcerative colitis as different stages in one disease. Hewes[32] considered the two types to be entirely distinct but believed it possible for mucous colitis to become ulcerative. There is some clinical evidence in the present study which confirms the experimental findings and leads us to believe that in a certain proportion of cases of ulcerative colitis, mucous colitis serves as an etiologic factor. In 4 of the 13 patients there was a definite history of mucous colitis, which had existed from two to eight years. Associated manifestations of autonomic imbalance were present in all 4. Following an acute upper respiratory infection, the symptoms and clinical evidence of the more severe disorder appeared. In 1 patient not included in the present series a definite transition was noted in the course of two examinations made at an interval of a year. There was a history of bowel disturbance for many years, with the frequent passage of soft, mushy stools containing much mucus. These were associated with psychic disturbances and evidence of autonomic imbalance. The mucosa presented an appearance usually ascribed to this condition, a glazed, somewhat granular membrane to which clumps of tenacious mucus were adherent. During the year which followed the first examination he made no attempt to modify his diet or to alter his personal routine, and he returned with a marked aggravation of symptoms. The mucosa at this time was deeply congested and boggy, and a few pinhead-sized

ulcers were scattered over the surface of the rectum and sigmoid. Following the administration of calcium and careful dieting, he writes that he is usually symptom-free.

With the exception of features attributable to a neurogenic disturbance, the clinical manifestations of the patients in whom ulcerative colitis was apparently secondary to mucous colitis did not appreciably vary from the remainder in whom no similar etiologic basis was present. The response to treatment of the two groups showed little variation. However, the group termed secondary, after clinical recovery and healing of the mucosa, displayed occasional evidence of bowel disturbance in the nature of mushy stools or the passage of mucus. A frank return to the previously existing mucous colitis was not observed.

Conclusions. 1. Experimental calcium studies in a group of patients with mucous colitis and in another group with ulcerative colitis, together with certain clinical features observed, suggest that in a number of cases the ulcerative lesions are secondary to a long-standing mucous colitis.

2. The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the beneficial effect of calcium on the following existing conditions: (*a*) Nutritional change in the tissues, with or without a disturbance of calcium partition; (*b*) spasticity of the colon; (*c*) hemorrhage.

3. Calcium lactate or gluconate by mouth and parathyroid extract intramuscularly were administered to a group of 13 patients with ulcerative colitis. Eleven became clinically well in from four to eight weeks. Ten of these were observed over a period of from one to two and a half years. The mucosa of the lower bowel resumed a normal appearance in 8. Return of symptoms for a short period occurred in 2.

4. The clinical and anatomic improvement, which followed rather promptly the administration of calcium and parathyroid to patients with ulcerative colitis after other forms of therapy had been unsuccessful in several of them, seems to warrant the continued use of and further observation on the effects of this form of treatment.

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STAPHYLOCOCCUS SEPTICEMIA.

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The opinion appears widespread that invasion of the blood stream by the staphylococcus is a relatively benign affair and of rare occurrence. It is well known that staphylococci, more particularly the Staphylococcus albus, are constantly found on the skin and frequently in the body orifices, and it would seem likely that many of the profession, realizing the almost ubiquitous nature of these bacteria, conclude therefore, that their pathogenicity is low. Lillie and Stevens,[1] for example, comment that "the finding of the staphylococcus in the blood stream is rather unusual; not many such instances are reported." Yet the records of the Jewish Hospital for the last nine years show 18 cases of septicemia due to this organism, of whom 14 died (one subsequently in another institution). Four additional cases that ended fatally have not been included. In 3 there were lesions whose culture showed the staphylococcus, but whose blood cultures were negative. The fourth patient grew organisms from the blood culture thought at first to be Staphylococcus aureus, but whose morphologic characteristics were not typical.

Septicemia, as Boyd[2] points out, is a familiar term, "and yet when we analyze it we find it difficult to define." Thus in the strict bacteriologic sense, "any condition in which microörganisms circulate in the blood" would fall within the definition, but from a broader concept it is better to view a septicemia as characterized not only by bacteria in the circulating blood, but also by the development of certain clinical manifestations of their presence (such as pyrexia, petechial hemorrhages). A bacteriemia undoubtedly exists at times in many healthy individuals without the development of an actual infection.

Staphylococci most frequently enter the blood stream through skin lesions, such as boils, carbuncles, abrasions or burns; less often through infections in the mucous membranes of the ear, nose and throat, the gastrointestinal tract, urethra, uterus and possibly the lungs. In 50 cases (including our own) quoted in recent literature, the portal of entry is noted in Table I.

Opie[3] has shown experimentally, that staphylococci injected into the circulating blood accumulate in the lungs, where they are ingested by polymorphonuclear leukocytes; and in the liver and spleen where a similar process is initiated by endothelial and other mononuclear cells (Kupffer cells) as well as phagocytosis by poly-

morphonuclear leukocytes. Then too, as emphasized by Martin,[4] masses of bacteria often lodge in the large venous capillaries of the metaphyses of long bones in young individuals, where they are either taken up by the capillary endothelium or produce the lesions of osteomyelitis. Brickner[5] affirms that there are reasons for believing that distant bone processes are often due to metastases "that took place long before, namely, at the time of the acute hematogenous invasion." Metastatic abscesses occur in a large percentage of the cases and may greatly alter the clinical picture. Frequently these bone lesions serve as foci from which showers of bacterial emboli pervade the circulating blood during exacerbations; or there may be long periods of remission with a subsequent reawakening of a "dormant" infection by an apparently insignificant injury. "Thus reactivated, they may produce a more or less violent recrudescence of the disease, or, more commonly, may reveal their presence by some milder process of suppuration or necrosis." (Brickner.[5])

TABLE I.

Carbuncles, furuncles, and miscellaneous skin infections	26
Ear	4
Tooth extraction	1
Mouth operation	1
Tonsillitis	4
Respiratory infection	2
Abortion	4
Kidney operation	1
Unknown	7
Total	50

It is believed that in many instances "the blood stream may serve merely to transmit the bacteria" (Hammond[6]), and unless the attempt is made just at the time when showers are occurring, the blood culture may prove negative. Undoubtedly this was true in one of our cases in which a long continued suppuration in the mouth was followed by abscesses in the axilla and in the thigh (Staphylococcus aureus) with marked bone production in the underlying femur. Blood cultures were sterile, but the patient eventually succumbed to a Staphylococcus aureus peripachymeningitis.

PROGNOSIS. We are reminded by Bowler and Boardman[7] that "the result of any infection depends upon two variables, the resistance of the host, and the invasive power of the organism." Actually it is more probable that when an organism, a constant parasite of the body surface, is found in the circulating blood, the resulting septicemia is due to a marked diminution of the normal resisting powers of the individual. If these powers are so reduced and the normal threshold (of resistance) so lowered, that organisms of relatively slight virulence gain entrance into the circulation, the prognosis is definitely more serious than in types of septicemia where

the causative organism gains entrance because of its relatively high virulence. It is on this basis that one would predicate the high mortality in staphylococcus septicemia (70 per cent according to Babcock[8]); and particularly those due to strains of staphylococci of ordinarily lowest virulence. So that just as septicemias due to the staphylococcus have a higher mortality rate than those in which the streptococcus is the causative organism, so the less pathogenic strains such as Staphylococcus albus may carry a more serious outlook than the more virulent Staphylococcus aureus.

Of 57 recently reported cases of staphylococcus septicemia (including our own) the outcome was as follows:

TABLE II.

	Cases.	Died.	Mortality, (per cent).
Staphylococcus aureus	38	22	57.9
Staphylococcus albus	8	5	62.5
Staphylococcus (unqualified)	11	8	72.7
Total			61.4

One can therefore hardly agree with Bartlett[9] that "the finding of the Staphylococcus albus in the blood is not particularly serious." In fact our statistics would bear out the statement of Stetson,[10] that, contrary to general belief, the staphylococcus is the deadliest organism in general sepsis. Peet,[11] Reed and Stiles[12] and others have stressed the almost invariably fatal termination of staphylococcus septicemia when secondary to furuncles, which concurs with our experience at the Jewish Hospital where there were 7 such cases, of whom 6 died.

TREATMENT. An unbiased inquirer is immediately struck, and proportionately handicapped, by the numerous therapeutic measures that have been advocated. Disregarding those of obviously little potency, the procedures of chief popularity in the present-day literature dealing with the subject, may be grouped as follows: (1) Supportive measures, such as blood transfusions, infusions of glucose and saline solutions, ultraviolet therapy, and so forth. (2) Surgical measures designed to drain or remove the original focus of infection, or evacuate metastatic abscesses. (3) Administration of substances designed to directly combat the infection, such as mercurochrome, gentian violet, transfusion of immunized blood, staphylococcus vaccine, staphylococcus antitoxin, bacteriophage, nonspecific foreign proteins, and so forth.

Since the occurrence of the sepsis denotes the slight resistance on the part of the patient, a fundamental factor in treatment is the employment of such measures as will raise the resistance, "hoping," as Barker[13] says, "that the body will develop sufficient immunity to overcome the organisms in the blood stream." In view of the great prostration and marked weakness, together with the extreme

toxemia, the early administration of blood transfusions, frequently repeated, sometimes alternating with glucose and saline infusions, are strongly indicated. Stetson[10] in urging the transfusion of whole blood, states that in these conditions it is of two-fold value, because of (1) its power "to overcome the secondary anemia and build up the general condition of the patient," and (2) "the direct bactericidal action of the fresh blood on the infecting organism." Complete physiologic rest is absolutely essential, and ultraviolet therapy, while not curative, is at times of value.

Treatment of the local focus, by surgical means or otherwise, is usually imperative, to prevent reflooding of the blood stream with bacteria. The evacuation of abscesses, be they primary or metastatic, should be performed with the minimum of trauma.

In the past six years, numerous articles have appeared lauding the results of intravenous injections of certain dyes, the most popular of which being mercurochrome and gentian violet. Many observers feel that the beneficial effects following the intravenous injection of chemicals, is due to the induced violent systemic reaction, comparable to the phenomena seen after the injection of a foreign protein. It is a moot point how much of the improvement said to follow the injection of these dyes is due to the bactericidal or bacteriostatic action of the drug, and how much is due to the toxic effect on the body cells, especially those of the reticuloendothelial system. Young and his coworkers[14, 15, 16] have reported a series of cases treated with mercurochrome, with remarkable improvement, but only isolated reports have appeared from other investigators, the consensus of opinion being that gentian violet is of greater value in combating the Gram-positive staphylococci. Two of our patients receiving mercurochrome died, 1 six hours after his initial injection.

The researches of Churchman[17] showed that gentian violet has a bacteriostatic effect upon the staphylococcus, but that its effect in the blood stream is transitory, disappearing before two hours have elapsed. He furthermore points out that he was never able to kill organisms circulating in the blood by the intravascular injection of this dye. Despite this note of conservatism, many glowing claims for its efficacy have been made by subsequent observers. Young and Hill[18] write enthusiastically of its value, and Horsley,[19] Lillie and Stevens,[1] and Reed and Stiles[12] cite further examples of its alleged worth. On the other hand, Barker[13] is not in the least sanguine, Bean[20] lost 3 patients in whom it was used, while Babcock[8] feels that it "has a limited value." In our own series, intravenous injections of gentian violet (on the recommended basis of 5 mg. per kilo of body weight), were employed in 2 cases, both of whom died. At the present time, therefore, I believe we are quite justified in saying that its value is problematical.

In theory, the use of blood transfusions from immunized donors

has much to commend it, and Bowler and Boardman[7] and Hooker[21] who tried it in a small series, feel that definite improvement followed its use. Unfortunately, by the time a vaccine has been made, and a sufficient number of injections given to the proposed donor, so many days have intervened as to make the subsequent transfusion available at too late a date to be of value in the acute group that require it most urgently. However, in the chronic type, it promises more, but there have been difficulties in employing it in a conclusive number of cases.

The rationale of the employment of vaccines in the acute form of staphylococcus septicemia is open to grave doubts. With the body all but overwhelmed by the bacterial invasion, it is difficult to understand how additional antibodies can be evoked by vaccine administration. Here again it is in the chronic type that its use seems at times indicated. Mueller[22] and Watson[23] report several cases in which a favorable response was produced; and 2 patients in our series were apparently benefited, 1 by six, the other by thirteen injections; but 2 others succumbed, 1 to a pemphigus, the other to abscesses of the lungs and kidney. Although Hammond[6] and Horder[24] question their value, I am in accord with the views of Schauffler[25] that autogenous vaccines, while not curative, are at times helpful in the chronic cases.

Since the protective antisera obtained from immunized animals depend upon the production of soluble toxins by the specific organism injected, much doubt has been cast upon the efficacy of staphylococcus antitoxin, due to the fact that the staphylococcus does not regularly produce a soluble toxin. However, the discovery that certain strains of staphylococci do produce an exotoxin, has led to the manufacture of a product of supposedly definite potency. In 1 of our patients, a case of encephalitis, in which the Staphylococcus albus was isolated from the blood and the cerebrospinal fluid, eighteen injections of staphylococcus antitoxin (Lilly), given intramuscularly, intravenously and intraspinally, were the apparent cause of the cure. Encouraged by this result, an intravenous injection was given to a patient showing staphylococci in both blood and cerebrospinal fluid, but he died the day after his admission to the hospital. In another patient with a fulminant infection, and Staphylococcus albus in the blood culture, seven injections of the antitoxin failed to influence in the slightest his rapid downward course.

Since the work of d'Herelle[26] on the bacteriophage, several articles by Greenbaum and Harkins,[27] Rice[28] and others, have appeared, extolling its potency in numerous infectious processes, but with as yet questionable success in septicemia; in fact, Rice reports 2 cases, both treated without avail. Meleney[29] invites our attention to the fact that at present we have no definite measure of the importance of bacteriophage as an aid to the body against disease; and the

Journal of the American Medical Association[30] sounds a note of caution that the "whole subject is still in the experimental stage."

Nonspecific foreign proteins were employed unsuccessfully in 2 of our cases, and there is little in the literature to encourage its further use. It is indicated, if at all, in the chronic group, where its value is probably distinctly inferior to autogenous vaccines.

It is obvious that as yet no method has produced consistently satisfactory results. Until some more specific therapeutic measure is developed, therefore, our chief hope of lowering the mortality rate would seem to be in prophylaxis. Since half of these septicemias originate in infections of the skin, a marked advance should be made with the education of physicians and laymen relative to the proper treatment of these lesions. Squeezing and pricking furuncles, plucking hair from an infected follicle, and similar popular and time-honored procedures, should be strongly condemned, and conservative measures should be adopted until the body cells are able to throw their "wall of defense" around the invaded area. With our renewed attention directed toward the adequate sterilization of milk, and the increasing interest in the rational treatment of infected tonsils and nasal sinuses, the death rate from staphylococcic gastrointestinal and respiratory infections should be materially reduced.

Summary and Conclusions. Staphylococcus septicemia, far from being a disease of relatively benign import, is a condition fraught with the gravest consequences to the individual. Because of the severe constitutional symptoms, the formation of multiple metastatic abscesses and, too often, the fatal outcome, the prognosis is serious. This is true more emphatically if the focus of infection cannot be removed or sterilized; and although many patients in the more chronic group do not die, some of them certainly seem never to get well.

Although final conclusions from the small series of patients observed might be misleading, it is obvious from our mortality rate, which parallels that cited by others, that the treatment is highly unsatisfactory. This is due, in part, to the interval elapsing between the onset of the disease and a definite diagnosis. Frequently, once the diagnosis is established, valuable time is lost in essaying remedies of questionable potency. Only too often the onslaught is so fulminant that all measures seem unavailing.

Certain enthusiasts have, from time to time, reported striking cures with widely varying therapeutic measures, due in large part, probably, to variations in virulence of different strains of staphylococci. A critical analysis of present-day treatment of staphylococcus septicemia would seem to indicate that:

1. Days, often weeks, elapse, during which pyrexia, chills and other suggestive signs of septicemia, are not intensively studied.
2. Blood cultures in suspected cases should be made at the earliest

possible moment by a capable bacteriologist. In the event of a negative culture, the procedure should be repeated at frequent intervals until a bacteriemia is ruled out.

3. As soon as the staphylococcus is cultured from the blood, vaccination of a suitable donor should be begun, so that transfusions of immunized blood may be given at the earliest practical moment. However, blood transfusions from a nonimmunized donor may have a bactericidal action, and should be instituted at once.

4. While the value of staphylococcus antitoxin is still in doubt, its use in large amounts intravenously, intramuscularly, and if indicated, intraspinally, should be pursued, pending the immunization of a donor.

5. In chronic cases only, the employment of staphylococcus vaccine is at times attended with improvement.

6. Any necessary surgical maneuvers should be performed with minimal trauma, and such general measures as are essential for maintaining the patient's strength should be employed.

7. In our present state of knowledge, the value of the intravenous use of dyes, bacteriophage, or nonspecific foreign protein, must be considered problematical.

8. Prophylactic measures, at the present time, offer our greatest hope in materially lowering the mortality rate.

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THE INVOLVEMENT OF THE CORONARY ARTERIES IN ACUTE RHEUMATIC FEVER.

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A brief report of a clinical example of the recently much discussed involvement of the arterial system in acute rheumatic fever, especially as appertaining to the coronary arteries was recently published.[1] The point of interest was the invasion not of the small coronary branches but of the larger-sized vessels of this system so as to produce a symptomatology which has come to be recognized as meaning a closure of one of these branches. Many examples have come to notice since this publication but because of insufficient data and perhaps the doubt which may be shed on the diagnosis, they have been omitted from this series. In all, 3 cases will be described, fortified by electrocardiographic evidence which would seem to verify the suggested diagnosis and further comment made

on clinical observations resulting from these interesting examples. The first case has been previously described but important data added which would better clarify the problem.

Case Reports.—CASE I. M. G., female, aged thirty-six years, married, was admitted to the hospital on January 10, 1928. She had been in the hospital three times previously for purely surgical conditions. Her medical history was negative and never until the present complaint did she have symptoms referable to the cardiovascular system. Six months prior to the last admission she noticed slight dyspnea, precordial distress, epistaxes, weakness, pallor and progressive loss of weight. On January 7, 1928, or three days before admission, she was suddenly seized with an excruciating pain in the epigastrium, radiating to the right anterior chest and right arm, relieved only by large doses of morphin. This pain continued to the time of admission on January 10. On entrance to the hospital she complained of lower substernal pain and dyspnea. At the same time she noticed pain on motion and touch of her right ankle.

Examination showed an adult female who was more or less in shock and in great pain. There was an anxious expression on her face and her forehead was covered with a cold perspiration. The throat was congested. The pulse was irregular, of poor quality, 48 per minute; the heart sounds were poor in quality, slow and irregular and of the same rate as the pulse. There was slight enlargement to the left on percussion.

A diagnosis of partial heart block and acute coronary closure was made. The next day an enlarged tender liver was noted and a friction rub appeared to the left of the lower end of the sternum. Her temperature was elevated and a concomitant leukocytosis was present. From now on to January 21, 1928, one joint after another became swollen and tender. During this time she had frequent nosebleeds and an irregular fever. All her symptoms subsided on the administration of salicylates. She felt well until the twenty-fifth of the same month when again her temperature rose, epistaxis recurred and her joints were involved. Her response to salicylates was prompt, and on the last day of the month of January, 1928, her temperature became normal. A soft systolic murmur had appeared at the apex, and the heart showed a little widening. She felt well until February 21, 1928, when again she developed repeated epistaxes, an acute follicular tonsillitis, following which her temperature rose and the joints became successively swollen and tender. This lasted two weeks, with the same response to salicylates. Blood cultures, chemistry of the blood and Wassermann reactions were negative. The Roentgen ray never showed effusion in the pleural or pericardial cavities.

Comment. This case presented signs and symptoms which pointed to an acute coronary closure. It was observed that this patient developed distinct attacks of acute rheumatic fever which prompted the thought that there was a causal relation between the infection and the closure. The fact that this patient was sick for six months before the actual closure suggested the possible onset of the rheumatic condition then, and the closure occurred during the time of actual invasion of the heart by the rheumatic infection. Further light may be shed on the case at hand by referring to Fig. 1. In the publication referred to, the evolution of the S–T and T changes were not sufficiently stressed. It is important to do so in the light of recent articles which report isolated electrocardiographic finds in

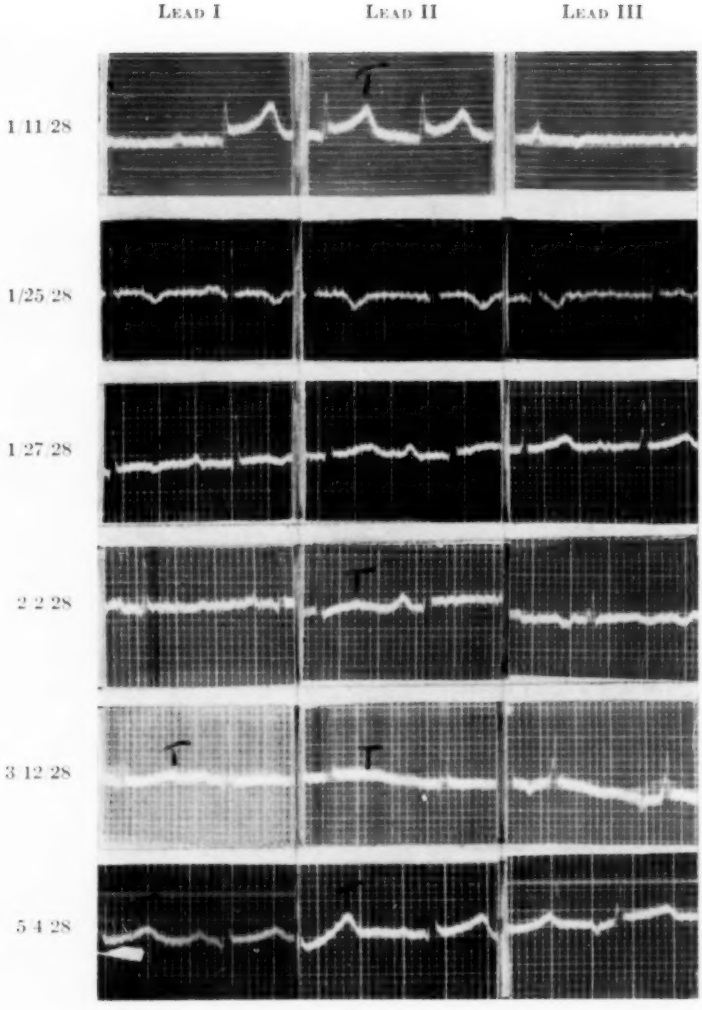

Fig. 1.

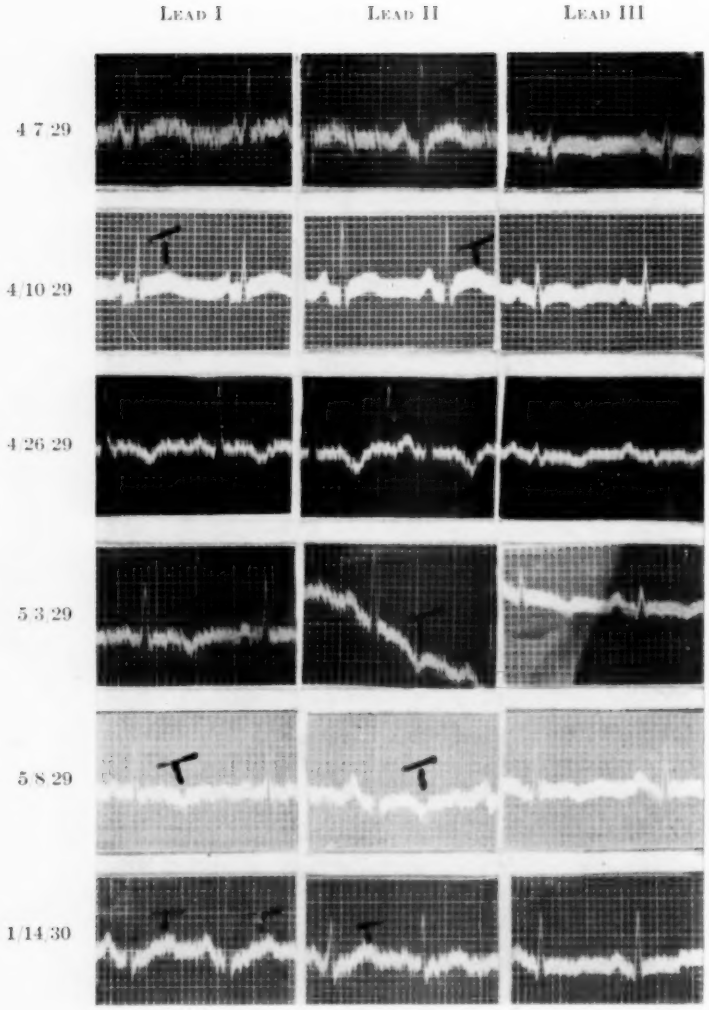

Fig. 2.

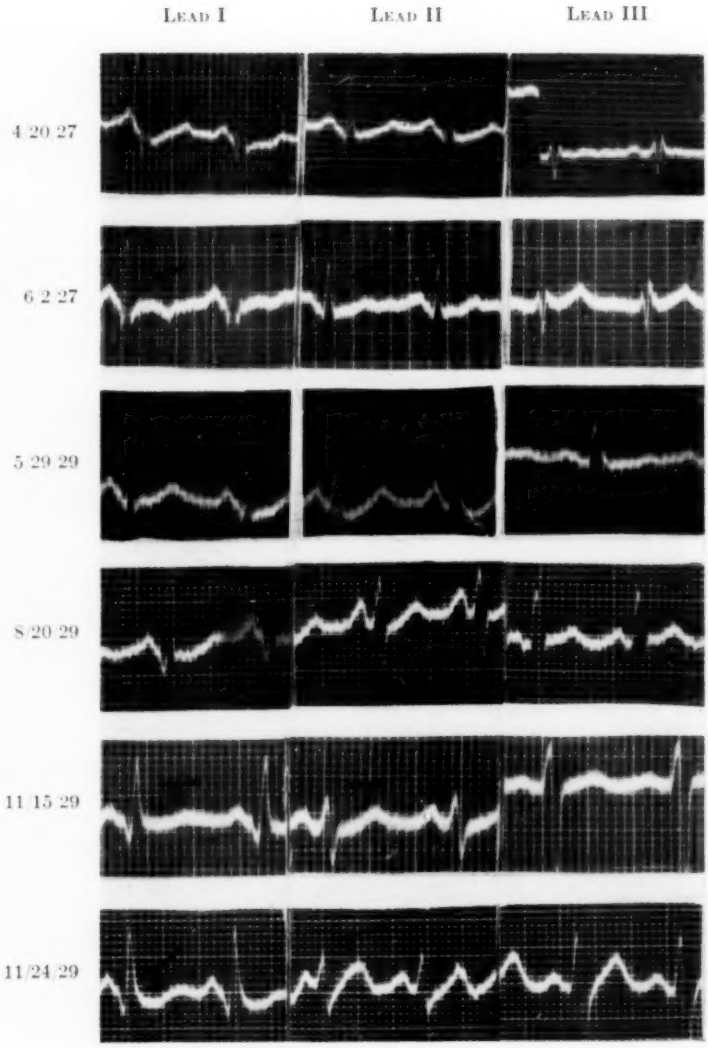

Fig. 3.

pericardial and pleural effusions similar to those seen in coronary artery disease. At no time did this case show clinical or roentgenologic findings suggestive of either of the above possibilities. The top tracing in this figure shows the high take-off of the *T* waves in Leads I and II. The record was taken three days after the attack and possibly represents a somewhat later stage of what might have been the monophasic curve seen in acute coronary closure. It is interesting to observe how the *T* wave became inverted two weeks later and remained so until February 2, 1928, when it showed signs of becoming upright. On May 4, 1928, the *T* wave was definitely upright.

Case II.—A. N., aged thirty-nine years, a druggist, was admitted to the Jewish Hospital of Brooklyn, N. Y., on April 6, 1929, and discharged May 12, 1929. His chief complaint was pain over the heart for eight days. His previous history was perfectly negative until three weeks prior to his admission, when he had a nosebleed. One week after this he developed a sore throat and fever, which compelled him to stay in bed for two days, after which the fever somewhat subsided. However he was not entirely well, having slight malaise and another nosebleed. His fever began to rise and he experienced pain in his right shoulder. In spite of this, he attempted work in his drug store, when suddenly, without physical or mental strain, he developed a constricting pain in the left midaxillary region, extending to under the sternum. However the pain was not severe enough to prevent him from continuing at his work; it was not associated with dyspnea, cyanosis, cold sweat or pain down the left arm. The pain continued throughout the day with little relief from opiates. He remained in bed for six days, after which the pain in the chest subsided. He sweated profusely during this time and complained of pain in the right shoulder. He did not take his temperature. On the morning before his admission to the hospital he suddenly developed a terrific crushing pain in the lower anterior chest more to the left. This time it was associated with dyspnea and cyanosis. He sweated profusely. The pain persisted throughout the day and with these complaints he was admitted to the hospital.

On physical examination there was found a poorly developed adult male, whose pertinent findings were as follows: the throat was markedly congested, the heart was regular and no murmurs were heard. There was no enlargement or displacement of the heart. The right shoulder was tender on motion and touch.

Clinical notes of his course in the hospital are as follows: On April 8, 1929, impaired resonance was found at the lung bases, more so on the right; percussion revealed no cardiac enlargement. On April 9, 1929, the heart action was regular and rapid and a gallop rhythm was present. There was no basal accentuation. There were definite signs of fluid at the right base and 35 cc. were removed. On April 10, 1929, he had another attack of pain in the precordium, viselike in character, associated with an impaired first sound. The next day a friction rub appeared over the heart; best heard over the lower end of the left border of the sternum. The flatness increased at the right base and 420 cc. of clear amber fluid were removed by aspiration. At the same time a small amount of fluid was removed from the left base, confirming the diagnosis of a bilateral pleural effusion. This fluid from the right base was thin and showed fibrous shreds on standing. The fluid from the left base was similar in character. These fluids were both examined and found to be exudates. Guinea-pig inoculation was negative for tuberculosis. Gallop rhythm was still present. On April 16, 1929, a note

was made by Dr. Rosenthal: "There is no evidence of pleural effusion, the heart is not enlarged. There is a blowing systolic present at the apex." On April 27, an intradermic injection of 0.2 mg. tuberculin was made, resulting in a negative reaction, local, focal and general. On May 11, 1929, all he showed was an impaired exercise test. After the first few days his temperature became normal.

Five different Roentgen ray examinations disclosed at no time any pericardial effusion. The last one taken on May 3, 1929, showed his chest normal. Blood counts done on April 8 and 16 showed 20,500 leukocytes and 12,600 leukocytes, with 79 per cent and 64 per cent polymorphonuclear leukocytes respectively. On April 27 the blood count was normal. The urine examinations were negative. The Wassermann reaction and the blood chemistry were normal. The electrocardiograms are shown in Fig. 2.

Comment. The electrocardiograms show the same interesting point which was demonstrated in Case I. The *T* waves of Leads I and II arise from the foot of *R* without any isoelectric period. It must be remembered that the first electrocardiogram was taken eight days after the initial insult. It seems likely that the take-off of the *T* would have been higher if the records were taken earlier. The *T* wave then begins to invert, following the rule, namely, the high take-off, then inversion of the *T* wave with an upward curving of the *R–T* or *S–T* interval. The *T* then becomes upright.

The later electrocardiograms which showed the inverted *T* waves were taken long after the effusions in the chest cleared up. This point should be emphasized, for it directs attention to the fact that the effusions in the chest seemed to have nothing to do with the abnormal electrocardiograms. There was no doubt that the heart was involved. The poor tone, the tachycardia, the soft systolic murmur at the apex, which appeared during the stay in the hospital, and last, the definite gallop rhythm, were all indications of this. The slight loss in cardiac reserve showed the remarkable amount of recovery at his discharge.

The suggested diagnosis was acute coronary closure. The symptoms and the electrocardiographic findings supported this. The underlying condition appeared to be an acute rheumatic infection. This was supported by the following symptoms: (1) repeated epistaxes, (2) an acute sore throat, (3) articular involvement, (4) pleural exudates and (5) the quick response to salicylates. Here again as in Case I, there appeared to have occurred an acute coronary closure during an acute rheumatic infection.

Case III.—J. G., aged thirty-six years, canvasser and born in Palestine, was admitted the first time to the Brooklyn Jewish Hospital on the service of Dr. Simon R. Blatteis on April 6, 1927. His family history was negative. In childhood he had measles, pneumonia and trachoma. Patient had been markedly obese all his life and suffered from dyspnea on this account. Just before his present complaint he had nosebleeds. His present illness began six days before admission, following exposure. He developed a sore throat and fever and the following day aches and pains in his muscles occurred. Then his joints became swollen and painful. First his knee

joints, then the ankles, then the shoulder joints became successively involved. Later other joints were infected. Associated with this there were profuse sweats.

The physical examination showed a very stout adult male with a flushed face, short neck and thick skin. He had emphysema. The heart sounds were distant but no murmurs or irregularities were noted. The various joints were swollen and tender. His blood pressure averaged 125 systolic and 85 diastolic. A leukocytosis was present. The Wassermann reaction was negative and the blood chemistry normal. The urine on one occasion showed bile and red blood cells. He had received massive doses of salicylates, responded favorably to therapy, and his fever subsided. An electrocardiogram taken during his stay will be discussed later. The man was discharged from the hospital on April 28, 1927, feeling better but not completely well. For this reason he was sent to a convalescent home. Because he still complained of joint pains, especially the right ankle, he came to the outpatient department on May 13, 1927. He was also troubled by dyspnea and profuse drenching sweats. The pain in the joints, the sweats and discomfort continued. On May 20 he experienced for the first time a dull substernal pain. He became dizzy and sweated profusely. At 4 A.M., on the morning of May 21, 1927 he was awakened from sleep by excruciating substernal pain, sweated profusely, became dizzy and almost collapsed; he also became very pale. Two hours later he had chilly feelings, his extremities were cold. The substernal pain became worse and he was readmitted to the hospital on May 21, 1927. He had received many doses of morphin. After admission he vomited several times.

Physical examination revealed a patient with an anxious expression and perspiring profusely. The throat was slightly congested. The heart showed some widening, but no thrill, murmur or irregularity was noted. There were distant heart sounds. The entire sternum was extremely tender as was the anterior axillary line. The patient complained of pain in the precordium the first few days in the hospital. On admission the blood count showed 18,400 leukocytes, with 65 per cent polymorphonuclears. The blood pressure went down to 86 systolic, 58 diastolic and finally before discharge up again to 114 systolic and 76 diastolic. The urine was negative. The electrocardiogram taken on June 2, 1927, will be discussed later. His temperature was elevated the first six days. On May 24, he had some pains in his left shoulder. He was put on salicylates to which he responded very promptly. After this he felt quite well for about a year, when he commenced to complain of attacks of dull substernal pain coming on with exertion and associated with dyspnea. These attacks were becoming more frequent and intense during the year previous to his next admission. At the same time he complained of pain in his joints off and on but never very severe.

On the night before his third admission, May 28, 1929, the patient was awakened from sleep by substernal pain and dyspnea and was admitted to the hospital again. The pain was so severe that repeated injections of morphin had to be given. The next day he had a milder attack. The heart showed some widening, poor heart sounds but no murmurs or arrhythmia. The pulse and temperature were elevated for six days, after which they became normal. An electrocardiogram was taken on May 29, 1929. The Roentgen ray of the heart showed a slight increase in the transverse diameter of the heart and no effusion in the pericardial cavity. The chest is of the sthenic type. The blood count on admission showed 14,700 leukocytes, with 75 per cent polymorphonuclears.

He made a good recovery and was discharged on June 11, 1929, following which he went to Sharon Springs. He felt well and worked hard until August 20, 1929, when he had another attack and was readmitted to the

hospital. The heart showed no murmurs or irregularities. His temperature was elevated for four days. The blood pressure on admission was 90 systolic, 68 diastolic, and on discharge 110 systolic and 82 diastolic. The leukocyte count on entrance was 22,200, with 73 per cent polymorphonuclears. An electrocardiogram was taken on the day of his admission and he was discharged September 6, 1929, feeling better, being then placed under the care of the cardiac out-patient department and his condition watched. He complained of substernal pains on exertion and did not do well and was sent to the hospital for the last time on November 3, 1929, because of another severe attack and was discharged December 3, 1929, feeling better.

Comment. This man was admitted to the hospital the first time on April 6, 1927, and discharged April 28, 1927, with an unquestionable diagnosis of acute rheumatic fever. His previous history did not show any symptoms suggestive of angina pectoris. After his discharge to a convalescent home and while still complaining of joint pains and profuse sweats, he was suddenly seized with an excruciating attack of substernal pain on May 20, 1927. This was associated with a drop in blood pressure and a leukocytosis, and fever. This was interpreted as being due to an acute coronary closure. Unfortunately an electrocardiogram was not taken until June 2, 1927, twelve days after the initial insult.

The heart showed no murmurs, no effusion in the pericardial cavity and no irregularities. After this he felt well for a year. This case emphasizes the point observed in all cases reported here and those omitted from this report for what seemed insufficient data, namely, that this complication in acute rheumatic fever offers a relatively good prognosis.

This case illustrates again the absence of clinical endocardial involvement. It accentuates the point that the coronary arteries have received the brunt of the invasion by the rheumatic virus. The later attacks represent either milder attacks of the same nature with the same underlying condition or the sequel mentioned previously.[1] The pains on exertion are interpreted in that light.

The electrocardiograms in Fig. 3 show points of interest but unfortunately, because their importance was not recognized in 1927 as at the present time, tracings were not taken in frequent sequence. His first electrocardiogram was taken April 20, 1927, during his acute rheumatic infection and it showed a depression of the R–T interval. The second was taken June 2, 1927. This showed a coronary T wave in Lead I, that is, a dipping down sharply of the T, preceded by an upwardly curved S–T interval. But it is reasonable to suspect that if this curve had been taken twelve days before, or at the time of the acute insult it might have shown the high take-off as in Cases I and II. The supposition here is that this tracing represents a definite stage in the evolution of this type of curve. It is to be noted that the timer was registering in 0.02 seconds. On May 29, 1929, the electrocardiogram shows abnormal S–T intervals and widening of the R in Lead II. On August 20, 1929, the S–T of Leads I and II are abnormal and the T of Lead I also.

The last tracing shows marked abnormalities, such as a deep *Q* in Lead I, widened main complexes and the oppositely directed *T* waves indicative of intraventricular conduction disturbances. These electrocardiograms, while not followed as satisfactorily serially as in the other 2 cases, nevertheless exhibit the gradual changes in the myocardium following the initial insult.

The impression in this case was that here also had occurred an acute coronary closure during an acute rheumatic infection, but that myocardial damage followed the closure, which closure it must be remembered seemed to be due to the underlying rheumatic infection, producing rheumatic coronary arteritis.

Discussion. The 3 cases cited above in such detail were for the purpose of emphasizing the points brought out in the previous publication. They also serve to amplify moot points concerning the etiologic factor and also the meaning of the electrocardiographic findings. In addition certain clinical observations obtained from this interesting complication might be mentioned.

Papers have been published in which isolated curves resembling the coronary *T* wave were shown. This appeared in conditions other than coronary artery disease, such as pericarditis and pericardial effusions, showing coving and the inversion of the *T* waves. It is also true that a high take-off of the *T* waves from the *R* may occur in isolated curves. Such tracings have been reported in pneumonia and other conditions. But it is the conception of the author, supported by the experimental work of Smith, that these curves when they follow an orderly arrangement, such as a high take-off following which the *T* wave becomes sharply inverted to again become upright at some subsequent time, have not occurred in any other condition except that of coronary closure, whatever its cause. The cases reported suggested strongly the diagnoses of acute coronary closures in view of the symptoms such as collapse, pericardial friction rub, leukocytosis and fever.

The point to be brought out particularly is the occurrence of the acute coronary closures during a very active acute rheumatic infection. The diagnosis of acute rheumatic fever seemed warranted in all of these cases. The closures occurred during the active stage of the infection, for the reason that the larger branches of the coronary system were involved by the rheumatic virus. The pathology underlying the arterial involvement has been previously discussed in detail.[1] Further proof is appearing in the literature showing that in acute rheumatic fever the vascular system is extensively involved. It should be mentioned in this connection that in all 3 cases there had occurred repeated epistaxis, a fact explainable on the basis that this was merely a local phenomenon of the vascular involvement, exemplifying that which took place in the heart.

Another point in common in all 3 cases was that the endocardium received practically none of the brunt of the attack of the rheumatic virus. In other words, the myocardium was principally involved.

This peculiar localization was due only to the fact that the coronary system was much more involved than usually occurs in the acute rheumatic fever.

Another phase of this interesting problem was the relatively good prognosis. All 3 cases survived a very acute closure of the coronary artery. This fact carries with it the reason, perhaps, for its not having been recognized before. Very few cases have come to autopsy.[1]

The patients in this series were all adults. Even those cases not included in this series were all grown-ups. It is possible that the condition occurs mostly in adults because they have a greater arterial vulnerability.

As to the nature of the closure, it is not felt that it need necessarily be a thrombosis, but that the specific lesion in the vessel may be the site of considerable edema, as in any exudative condition, and that this may account for the closure. A thought that this brings up is that perhaps the larger vessels of the coronary system are much more frequently involved than has been hitherto suspected; but in view of the fact that the thrombosis does not occur in most of the cases and likewise because the lesion may not be large enough to produce a complete closure, the picture that we described above does not occur so frequently.

In conclusion, it is to be emphasized that during an acute rheumatic infection any bloodvessel, small or large, may possibly be involved; that those of the heart may likewise be involved; that when the larger coronary branches are affected under certain circumstances it may be sufficient to encroach so upon the lumen as to occlude it; or a thrombosis may occur secondarily, producing a closure. When the closure occurs these patients experience excruciating pains indicative of the lesion. This closure occurs during the acute active stage of the rheumatic infection when one would suspect marked involvement of the myocardial vessels. Furthermore, these patients usually get well. Occasionally as in the last of these patients there is a sequel in the nature of an angina pectoris syndrome. This possibility has been mentioned in the previous publication. The electrocardiographic findings followed those produced experimentally, and did not represent an isolated finding but showed a definite development of the inversion from the high take-offs of the *T* waves. This is best seen in the first 2 cases.

Summary. 1. Three cases of rheumatic coronary arteritis with closure are reported.

2. The symptomatology and the prognosis are discussed.

NOTE.—I wish to take this opportunity to thank Drs. Simon R. Blatteis, Alex L. Louria and Joseph Rosenthal, on whose services these cases occurred, for the privilege of reporting them.

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LOW-VOLTAGE T WAVES IN THE ELECTROCARDIOGRAM.*

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The clinical importance of inverted *T* waves of the electrocardiogram is well known. That inverted *T* waves may indicate myocardial involvement, that changes in the *T* wave may be characteristic of coronary artery thrombosis, that alone or in combination with other simple alterations in the record the *T* wave may give evidence of a myocarditis or a pericarditis, or even of a long-standing hypertension, are facts that have become common knowledge. However, no one has emphasized the significance of small *T* waves. If one considers for a moment that a *T* wave before it becomes inverted must diminish in size, it is apparent that low-voltage *T* waves may be as significant and have much the same clinical and prognostic implication as inverted *T* waves of the electrocardiogram.

Pardee,[1] in 1924, stated that a *T* wave less than 2 mm. in amplitude should be considered abnormal. The few cases of such an abnormality that have been published have appeared only indirectly when some other study has been under way. These isolated examples,[2,3] however, show that flat *T* waves may indicate severe myocardial or pericardial damage, and this has been confirmed by autopsy.

It will be shown that low voltage of the *T* wave, that is, *T* waves of not more than 1 mm.† in any lead, may signify severe myocardial involvement. Graphs containing *T*-wave inversions in Leads I and II and graphs of patients who had received digitalis have been entirely excluded from this study. In all, for the last three to four years 107 patients with such records have been followed, a great many of whom have had numerous electrocardiograms, some over a period of years. Of these, 89 were hospitalized and 18 were ambulatory. The cases fall into three categories: Group A, 24 patients who died, 12 of whom were autopsied at the New York Hospital, and the remainder of whom died either at the hospital or some time later at home; Group B, the remaining 65 hospital patients, 17 of whom returned for further investigation; finally, Group C, 18 ambulatory patients who attended the Cornell Clinic in 1928.

* Read before the Section of Medicine, New York Academy of Medicine, N. Y., May 20, 1930.

† The *T* wave may be of an amplitude of no more than 1 mm. in either Lead I or II alone and it is believed that this abnormality, too, is significant. Kraus and Nicolai[4] in 1907 suggested that this change indicated muscle disease.

GROUP A. 1. Twelve autopsy cases: Seven patients showed a myocardial fibrosis, 4 of whom had marked coronary artery disease (Fig. 1*a*). Three cases of chronic rheumatic cardiovascular disease, each showed an involvement of the myocardium and endocardium, and 2 of these showed a rheumatic pericarditis. The eleventh case had carcinomatous metastases to both the myocardium and pericardium and the twelfth was one of tuberculous pericarditis. (See Table I.)

TABLE I.—HOSPITAL PATIENTS WITH LOW-VOLTAGE T WAVES WHO WERE AUTOPSIED.

No. of cases.	Average age.	Clinical diagnosis.	Pathological diagnosis.
7	55	Degenerative cardiovascular diseases*	Fibrous myocarditis (marked coronary artery disease in 4 cases).
3	34	Chronic rheumatic cardiovascular disease	Rheumatic myocarditis and endocarditis (rheumatic pericarditis in 2 cases).
1	31	Tuberculosis	Tuberculous pericarditis.
1	17	Teratoma testis	Tumor tissue in myocardium and pericardium.

* Degenerative diseases: Fibrous myocarditis, arteriosclerosis, hypertension, coronary artery disease.

Myocardial damage was thus present 11 times. The pericardium was involved 6 times, twice with a coronary artery thrombosis, twice in rheumatic heart disease, once in a tuberculous heart and finally once in cancer. The myocardium or pericardium was, therefore, involved in 100 per cent of these cases.

2. Twelve deaths, no autopsy: The number of patients here, too, was 12, and, although no opportunity for pathological confirmation was present, 11 died with symptoms of typical myocardial failure and 1 of a pulmonary tuberculosis.

TABLE II.—COMPARISON OF DEGENERATIVE WITH RHEUMATIC HEART DISEASE IN 107 PATIENTS WITH LOW-VOLTAGE T WAVES.

	89 hospital cases.				18 ambulatory cases.	
	24 deaths.		65 discharges.			
	Frequency, per cent.	Average age, years.	Frequency, per cent.	Average age, years.	Frequency, per cent.	Average age, years.
Degenerative diseases .	58	55	28	52	89	51
Chronic rheumatic cardiovascular disease .	25	38½	35	33	11	40
Miscellaneous . . .	17	. . .	37			

Clinically the diagnoses were chronic myocarditis, 3; general arteriosclerosis and coronary artery disease, 2 (Fig. 1*b*); general arteriosclerosis, 1; general arteriosclerosis and hypertension, 1; chronic rheumatic cardiovascular disease, 3; pulmonary tuberculosis, 3. (See Table II.) (The pericardium was known to have been involved 4 times, twice in tuberculous and twice in rheumatic heart disease.)

TABLE III.—CLINICAL DIAGNOSES IN 107 PATIENTS WITH LOW-VOLTAGE T WAVES.

	89 hospital cases.		18 ambulatory cases.
	Group A 24 deaths.	Group B 65 discharged.	Group C
Chronic myocarditis	8	13	5
Acute myocarditis	..	2	
Myocardial insufficiency	3	2	
Arteriosclerosis	7	9	7
Hypertension	4	11	9
Angina pectoris	..	1	8
Coronary artery disease	2	..	8
Syphilis	..	6	1
Aortitis	..	2	
Auricular fibrillation	..	1	
Chronic cardiovascular disease	6	14	3
Mitral stenosis	5	13	
Mitral insufficiency	3	7	
Aortic insufficiency	1	6	
Acute rheumatic fever	..	10	
Pericarditis	8	8	
Tuberculosis	4	4	
Teratoma testis	1		
Pleural effusion	3	5	
Nephritis	3	3	
Exophthalmic goiter	..	5	
Pneumonia	..	5	
Bronchitis	..	3	

GROUP B. Patients discharged from the hospital: This group consisted of 65 patients, 17 of whom returned for reëxamination and electrocardiogram. One is immediately struck by the change in the type of case. (Tables II and III.) The occurrence of chronic myocarditis, general arteriosclerosis, hypertension and coronary artery disease, the most common diagnoses in the patients that died, are no longer predominant, but rheumatic heart disease prevails, particularly acute rheumatic fever. In other words, the patient with degenerative cardiovascular disease may die in the hospital, whereas the patient with rheumatic heart disease usually is discharged well. There were thus 32 patients of the entire 89 hospital cases who had degenerative cardiovascular disease. Fourteen of these died, giving a mortality rate of 44 per cent to this type of patient whose electrocardiogram contained a flat *T* wave. Since

this was a follow-up investigation, successful only in less than one-half the cases, the true mortality rate is probably higher. In the cases of chronic rheumatic cardiovascular disease the deaths were 6 in 29 patients, or 21 per cent. It seems evident, therefore, that nearly one-half of the hospital patients with degenerative disease of the heart and bloodvessels and with flat *T* waves will die within three to four years; that only 1 in 5 with a diagnosis of rheumatic cardiovascular disease will succumb within the same length of time.

The active rheumatic heart disease cases showed the most remarkable changes in the *T* waves. In the course of the acute rheumatic fever these waves were flat, becoming inverted as the patient became more toxic, or as a complicating pericarditis occurred, and returning to normal as the patient recovered (Fig. 2). The flat *T* waves here undoubtedly indicate a rheumatic infection of either the myocardium or pericardium, or both. The flat *T* wave became not only inverted during a pericarditis, but, as has recently been observed,[5] it occasionally took on the peculiar shape of the "coronary *T* wave" of Pardee[6] or the "cove-plane *T* wave" of Oppenheimer and Rothschild.[7]

Five cases of pneumonia (Fig. 3), 3 cases of bronchitis, 5 patients with exophthalmic goiter (Fig. 4) are included in this group and are of clinical interest. In hyperthyroidism, as the basal metabolism and the tachycardia increased markedly, the *T* waves became flat. In the extremely sick, therefore, a flat *T* wave was present. As the patient improved clinically and by laboratory tests the *T* waves became normal. Exactly the same condition was observed in pneumonia. Only very toxic pneumonia patients developed a flat *T* wave. Six cases of syphilis were also observed; 1 patient who returned for reëxamination and who had received intensive antiluetic treatment since his discharge from the hospital presented a normal electrocardiogram, both the 4+ Wassermann reaction and the flat *T* wave having disappeared (Fig. 5). In regard to duration of life the prognosis is good, as not one of these patients with pneumonia, bronchitis, exophthalmic goiter or syphilis died.

Pleural effusions seemed to account for flat *T* waves 5 times.

Group C. Ambulatory patients: There were 18 ambulatory patients who were observed during 1928, for about six months only. The average age was fifty years. The clinical diagnoses were arterial hypertension, 9; coronary artery disease, 8; general arteriosclerosis, 7; chronic myocarditis, 5; angina pectoris, 8; chronic cardiovascular disease, 2; lues, 1; or combinations of these.

Eleven patients had more than one record taken. Of these 3 died within four months of the first record (Fig. 1*c*). In 5 others the flat *T* waves became upright as the symptoms, usually precordial pain, disappeared. The *T* waves of the remaining 3 cases changed also; twice inverted *T* waves became flat and once a flat *T* wave became inverted.

The ages and diagnoses were similar to those in the groups in which patients died.

The conclusions to be drawn here are that flat *T* waves in ambulatory patients are often found in those suffering from the degenerative cardiovascular diseases, that they may be of serious import and that they are usually transient. They belong to the patient who is recovering from an acute coronary artery thrombosis or to one whose arteriosclerosis of this vessel is progressing very slowly. On the other hand, a patient with rheumatic heart disease and a flat *T* wave is usually too acutely ill to be an ambulatory clinic patient; he is a bed patient.

Discussion. The evidence presented indicates that flat *T* waves are often associated with myocardial involvement in general arteriosclerosis or in arteriosclerosis of the coronary arteries, with or without thrombosis, or are found in rheumatic fever, with or without pericarditis. Whether it be the diminished contractile power of the diseased heart muscle or whether it be electrical imbalance caused by the involved muscle, the fact remains that flat *T* waves are usually associated with acute muscle inflammation or chronic degeneration.

That flat *T* waves occur in pericarditis may signify either that this condition alone, or that disease of the underlying myocardium, is the cause of the electrocardiographic abnormality. Yet it does occasionally appear that a pericarditis alone produces this flat *T* wave, as, for example, in the tuberculous pericarditis or in cancer of the pericardium, where the underlying muscle is only slightly involved. If this be true it might mean that the pericardium or the outer surface of the myocardium played an important rôle in production of the *T* wave.

In patients with severe hyperthyroidism, pneumonia or bronchitis the toxic products of the disease have probably affected the heart muscle. Previous writers[10,11,12] have reported large *T* waves in hyperthyroidism, but in this study it was observed that the extremely sick, that is, the thyrotoxic patients whose basal metabolism was increased by 50 to 100 per cent and whose pulse rate was 140 to 180 per minute, showed a flat *T* wave. (The records were all taken before iodin was given, as this drug tends to flatten the *T* wave.[12])

The flat *T* wave in lues may be due to a syphilitic involvement of the myocardium.

The flat *T* wave which becomes inverted during the development of a rheumatic pericarditis occasionally takes the form of the "coronary *T* wave" or "cove-plane *T* wave" that is customarily associated with coronary artery thrombosis. This would seem to indicate that this particular inverted *T* wave is not specific for coronary artery thrombosis, and it also suggests that a pericarditis, of whatever etiology, is responsible for it.

The explanation for the flat *T* wave in pleural effusion is not clear. It may be that tuberculosis of the heart muscle has been present. On the other hand, it may be that mechanical compression or rotation of the heart produces the flat *T* wave.[8]

Summary. In 107 patients a study was made of low-voltage *T* waves, that is, flat *T* waves, in which the amplitude in any lead is not more than 1 mm.

The 12 patients that were examined postmortem all showed definite myocardial or pericardial damage. The clinical diagnoses in 7 cases were chronic myocarditis, general arteriosclerosis, coronary artery disease or arterial hypertension. Chronic rheumatic heart disease was present in 3 patients, tuberculous pericarditis in 1 and carcinoma metastases to the pericardium in another.

Another group of 12 patients died but no autopsies were performed. Eleven died with typical myocardial failure and 1 of pulmonary tuberculosis. Since the clinical diagnoses here were very similar to the group in which autopsies were performed, and the ages were practically the same, in all probability similar damage to the myocardium was present.

Altogether, there were 89 hospital patients with flat *T* waves, the mortality among those with degenerative cardiovascular disease was at least 44 per cent during the course of a three to four years investigation.

Acute rheumatic infection of the myocardium or pericardium often produces a flat *T* wave, and in the progression of the disease the *T* wave may become inverted, or, if the patient recovers, it will become upright. The rheumatic cardiac patient with a flat *T* wave is acutely ill and is probably always a bed patient.

The so-called "coronary *T* wave" or "cove-plane *T* wave" that is customarily associated with coronary artery occlusion may appear in a patient with rheumatic pericarditis.

Suggestive evidence has been presented that pericarditis alone, without disease of the underlying myocardium, may cause a flat *T* wave.

Flat *T* waves are practically always transitory, becoming inverted as the myocardial or pericardial damage spreads and increasing in amplitude on cure or improvement.

In pneumonia, bronchitis, exophthalmic goiter and syphilis the flat *T* wave appears to indicate a very severe form of illness. Nevertheless, the patients here studied all got well. As recovery or improvement takes place the *T* wave becomes of normal amplitude.

Pleural effusions occasionally produce flat *T* waves.

A flat *T* wave is not uncommon in ambulatory patients. In a series of 18 patients of the latter type evidences of degenerative cardiovascular disease were present in almost 90 per cent. The flat *T* wave here was of serious import, indicating probably some severe degree of arteriosclerosis of the coronary arteries.

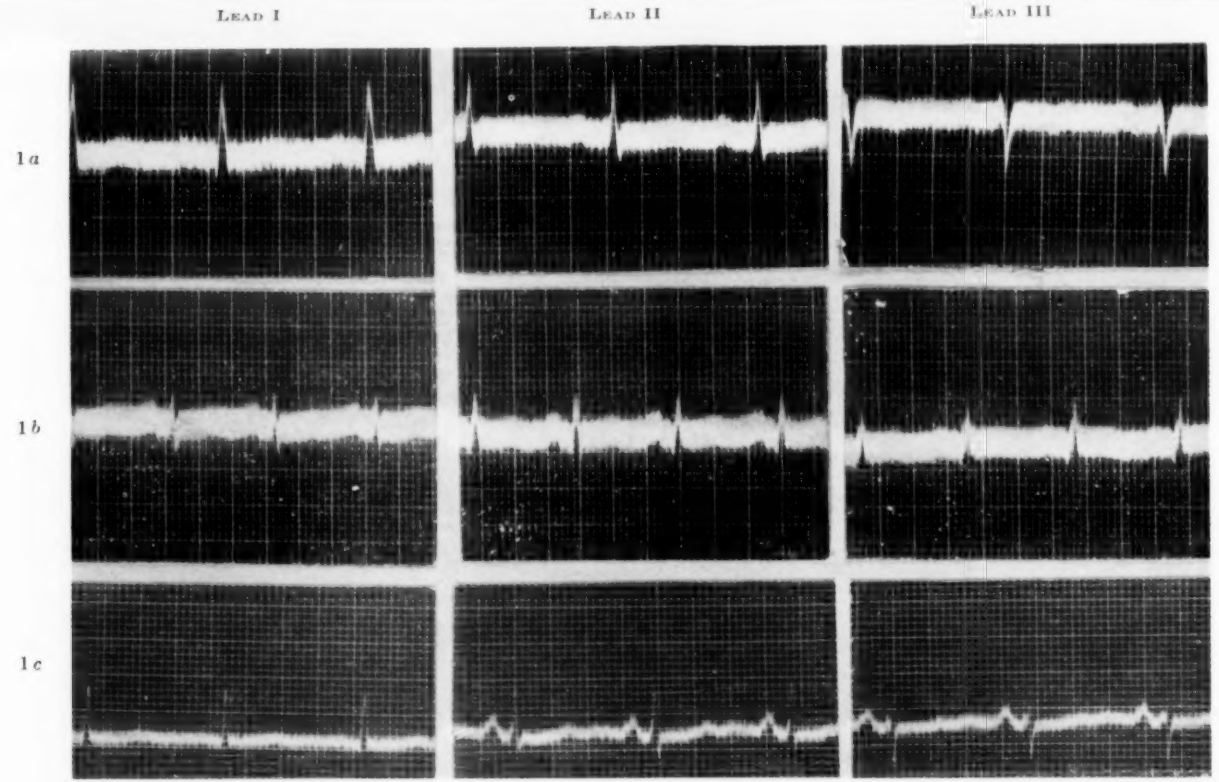

Fig. 1.—1*a* Patient H. S., aged seventy-four years. Arteriosclerosis, myocardial degeneration, angina pectoris. September 21, 1927, flat *T* waves. Died, October 29, 1927. 1*b*. Patient H. S. C., aged fifty-two years. Coronary thrombosis, general arteriosclerosis. September 2, 1927, flat *T* waves. Died, September 11, 1927. 1*c*. Patient G. R., aged sixty years. Ambulatory patient with hypertension, coronary artery disease. September 27, 1928, flat *T* waves. Blood pressure 180/120. Died, October 1, 1928, in an attack of "angina pectoris."

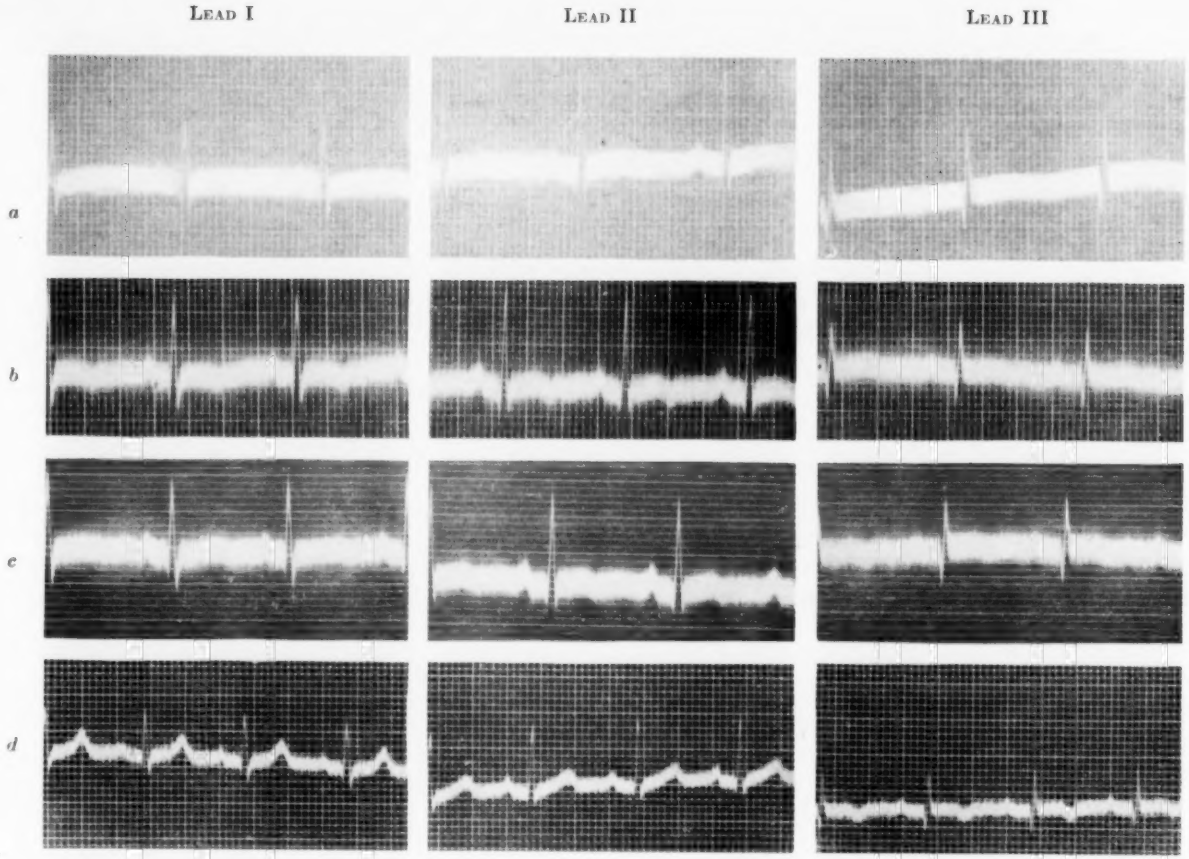

Fig. 2.—Patient A. R., aged seventeen years. Acute rheumatic pericarditis. (*a*) April 28, 1928, flat *T* waves in acute rheumatic fever. (*b*) May 5, 1928, *T* 1 and 2 inverted and "cove-plane"—acute fibrinous pericarditis. (*c*) May 12, 1928, beginning recovery of patient. *T* waves flat. (*d*) March 29, 1929, follow-up on patient, *T* waves normal.

FIG. 2.—Patient A. R., aged seventeen years. Acute rheumatic pericarditis. (*a*) April 28, 1928, flat *T* waves in acute rheumatic fever. (*b*) May 5, 1928, *T* 1 and 2 inverted and "cove-plane"—acute fibrinous pericarditis. (*c*) May 12, 1928, beginning recovery of patient. *T* waves flat. (*d*) March 29, 1929, follow-up on patient, *T* waves normal.

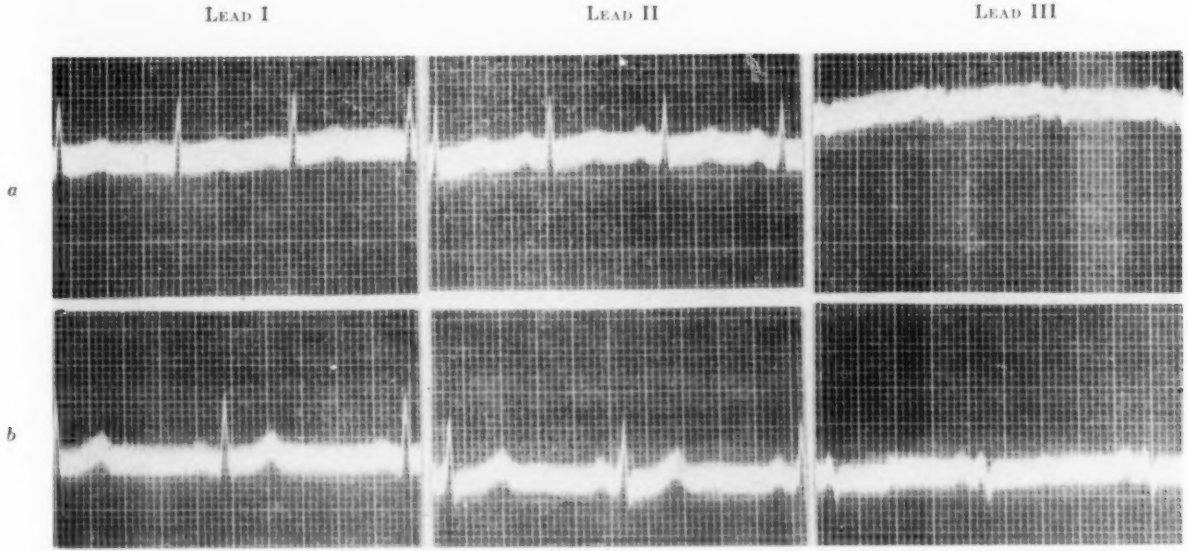

FIG. 3.—Patient J. G., aged twenty-four years. Bronchopneumonia. (*a*) December 12, 1927, flat *T* waves, pneumonia. (*b*) March 23, 1929, follow-up on patient. *T* waves normal.

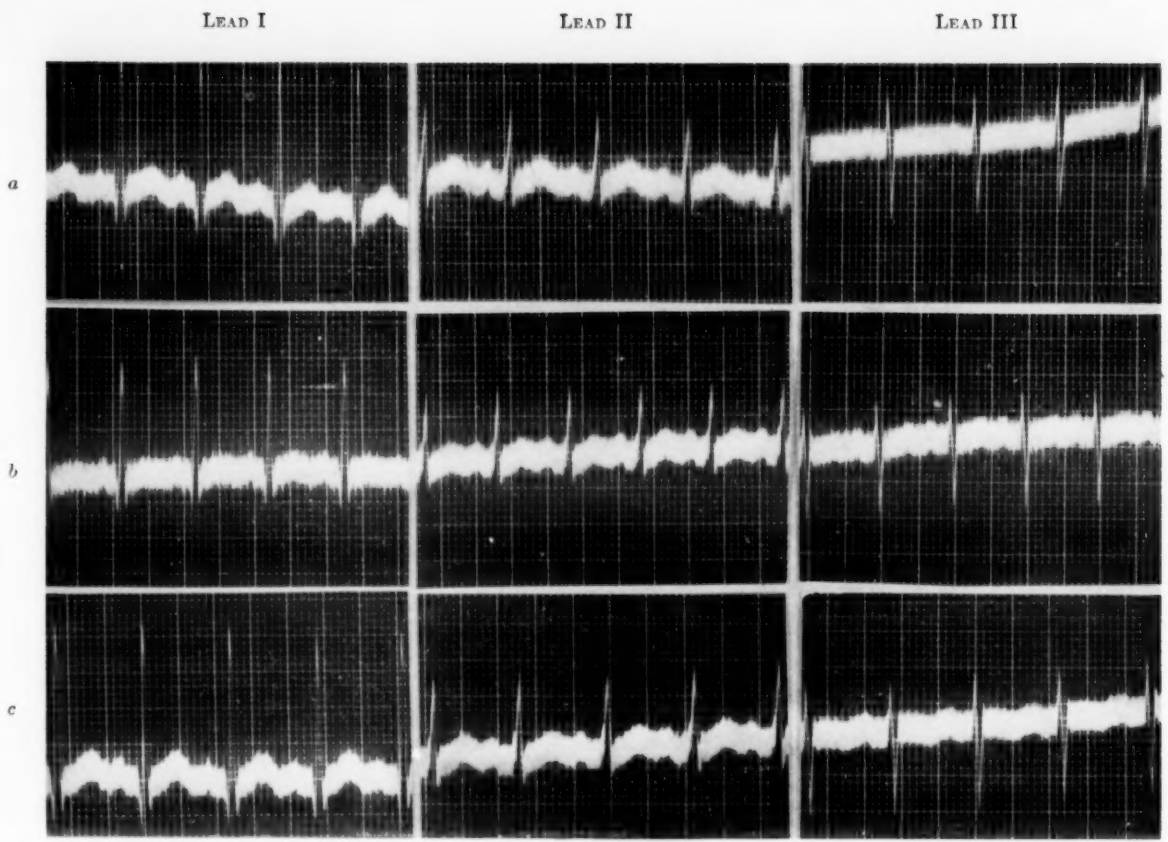

Fig. 4.—Patient C. D., aged seventeen years. Exophthalmic goiter. (*a*) July 5, 1927, rate 130 to 140 per minute. Basal metabolism +26. *T* waves normal. (*b*) November 9, 1927, rate 145 to 150 per minute. Basal metabolism +80. *T* waves flat. (*c*) December 19, 1927, rate 125 to 135 per minute. Basal metabolism +44. *T* waves normal.

Fig. 4.—Patient C. D., aged seventeen years. Exophthalmic goiter. (*a*) July 5, 1927, rate 130 to 140 per minute. Basal metabolism +26. *T* waves normal. (*b*) November 9, 1927, rate 145 to 150 per minute. Basal metabolism +80. *T* waves flat. (*c*) December 19, 1927, rate 125 to 135 per minute. Basal metabolism +43. *T* waves normal.

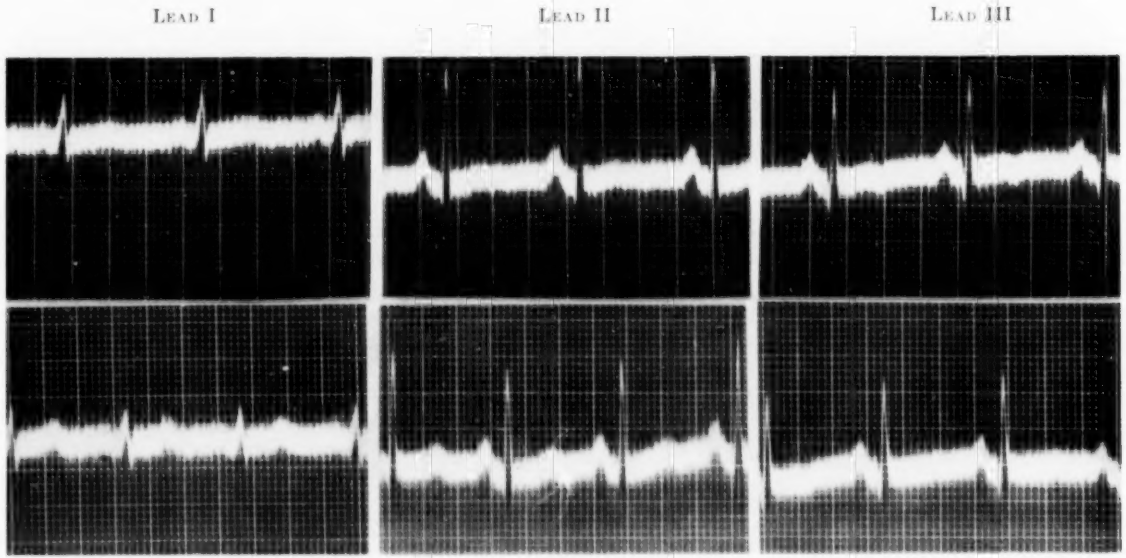

Fig. 5.—Patient T. V., aged thirty-seven years. Syphilis of bone and larynx. (*a*) August 11, 1927, flat *T* waves. Wassermann test 4+. (*b*) April 12, 1929, *T* waves almost normal. Wassermann negative after one and a half years antiluetic treatment.

A flat T wave in only Lead I or II, although not as significant as flat T waves in all leads, is of some importance, since it suggests that on further observation the T wave may become inverted.

NOTE.—I wish to express my sincere thanks to Dr. Lewis A. Conner for his interest in the work and for his many helpful suggestions. To Miss Lydia Buechi, Miss Roberta Maybin and to Miss Margaret Rochleau I am indebted for their help in collecting the data.

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THE HEMOGLOBIN CONTENT, VOLUME AND THICKNESS OF THE RED BLOOD CORPUSCLE IN PERNICIOUS ANEMIA AND SPRUE, AND THE CHANGES ASSOCIATED WITH LIVER THERAPY.

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IT is a rather general impression that in pernicious anemia the red cells are supersaturated with hemoglobin. This conception has probably arisen from the well-known fact that in this disease the so-called color index is characteristically greater than 1. Several

years ago Haden[1] pointed out that what is understood as the color index does not measure the hemoglobin saturation of red cells but rather their hemoglobin content. He coined the term "saturation index" to express the relation of quantity of hemoglobin to cell volume, and showed that in pernicious anemia the red cells are not supersaturated.

In earlier papers[2,3] the inadequacy and inaccuracy of the color index was discussed. It was pointed out that the term is vague and misleading, that the calculation is based on an incorrect standard for normal red cell count and variable standards for hemoglobin, the equivalent of 100 per cent hemoglobin in grams per 100 cc. of blood varying almost with each of the numerous instruments employed for its estimation. It was also pointed out that similar disadvantages are associated with the calculation of volume index and saturation index. It was therefore suggested that the hemoglobin content and volume of the red corpuscles be calculated directly without reference to any arbitrary standard of normal. Such calculations are simple, afford greater accuracy and increased clarity as compared with the indexes and, furthermore, fall in line with the present tendency to report hemoglobin directly in grams.

The volume, hemoglobin content and hemoglobin concentration of the average red corpuscle of any sample of blood may be very simply calculated when the red cell count, the hemoglobin and the relative volume of packed red cells in that sample are known.

The volume of the average red corpuscle, or *mean corpuscular volume* is determined by dividing the volume of packed red cells, expressed in cubic centimeters per 1000 cc. of blood, by the red cell count, expressed in millions per cubic millimeter. The resulting value expresses average corpuscular volume in cubic microns.

The amount of hemoglobin in the average cell or *mean corpuscular hemoglobin* is calculated by dividing the amount of hemoglobin, expressed in grams per 1000 cc. of blood, by the number of red cells (millions per cubic millimeter). The resulting value expresses average corpuscular hemoglobin in micromicrograms.*

The proportion of hemoglobin in the average cell or *mean corpuscular hemoglobin concentration* is determined by dividing the amount of hemoglobin (grams per 100 cc. of blood) by the volume of packed red cells (cubic centimeters per 100 cc. of blood) and multiplying the result by 100. The result is expressed in per cent. The constant derived by this calculation is useful rather than accurate in a physical sense, since it is assumed that hemoglobin is present in the red corpuscle in an aqueous solution.

In the papers already cited, normal values based on several hundred accurate blood determinations in healthy young men and

* A micromicrogram is a millionth of a millionth part of a gram or grams $\times 10^{-12}$; it is abbreviated by the Greek letters gamma ($\gamma\gamma$).

women residing chiefly in different regions of the United States were presented. These may be summarized as follows:

The normal mean corpuscular volume is approximately 85 cu. μ. Values above 95 cu. μ or below 75 cu. μ are probably abnormal and an indication of a pathologic state.[4] No significant differences in respect to the size of corpuscles were noted in the two sexes, but the values for residents of more northern districts of the United States were somewhat higher than for those residing in the South.

The normal mean corpuscular hemoglobin is 28 to 29 micromicrograms. Values above 31.5 micromicrograms or below 26.5 micromicrograms are probably abnormal. The normal mean corpuscular concentration is 35 per cent and values between 33 and 39 per cent are probably normal. No differences in corpuscular hemoglobin or corpuscular concentration were noted in respect to sex.

Value of Calculation of Physical Constants in Diagnosis. As early as 1903 Capps[5] pointed out that the variations in the size of cells seen in anemias were not the effects of osmosis producing larger or smaller cells but were the results of what he termed "biotic influences." He felt that a macrocyte rich in hemoglobin could not be produced by osmosis (which would result in the formation of a large pale cell) but is the product of abnormal cell development. These fundamental observations were little heeded, however, and it remained for Price-Jones[6] to first attract general attention to the value and importance of observing the physical changes in the red corpuscle associated with disease. As is now well known, Price-Jones noted in pernicious anemia a great variation in the size of the red cells, with a marked preponderance of large cells and a consequent increase in average cell diameter. The technique employed by Price-Jones in measuring the diameters of the cells is very tedious and time-consuming and entails the use of special apparatus. Recently, methods for the measurement of cell diameter have been greatly simplified but in so doing accuracy has been sacrificed for simplicity.[4] Probably the most popular method of measurement at the present time involves the use of a micrometer eyepiece. Even this method, which is at best only relatively accurate, requires much time and patience.

It is the object of the present paper to indicate the value of the calculation of corpuscular volume, corpuscular hemoglobin and corpuscular concentration in facilitating the diagnosis of pernicious anemia and sprue as well as in affording a clearer conception of the physical alterations in the red corpuscle in these conditions. The alterations which occur in conjunction with the remissions produced by liver therapy will also be discussed.

Material and Methods. A series of 100 blood examinations has been carried out in 16 cases of pernicious anemia and in 8 cases of sprue. The patients who form the basis of this study were all seen in the wards and Outpatient Department of the Charity Hospital

of Louisiana. In those suffering from pernicious anemia the diagnosis was made on the basis of characteristic history and physical and laboratory findings, including achylia gastrica, sore tongue, typical blood findings and neurologic changes. These cases were also identified by a prompt response to therapy, either in the form of liver diet or liver extract. In the cases of sprue the diagnosis was made on the basis of such characteristic findings as marked diarrhea, with or without typical voluminous frothy stools, emaciation, sore tongue, the absence of neurologic phenomena, and typical blood picture. Other possible causes of such symptoms and signs were as far as possible ruled out. The differentiation of pernicious anemia and sprue was in some cases difficult but for the purposes of this study such a distinction is not fundamentally important. The diagnosis of pernicious anemia or sprue was in each case concurred in by other clinicians. Doubtful cases are not included in this series.

Number of red cells, amount of hemoglobin and volume of packed red cells were determined in each case and from these values mean corpuscular volume, corpuscular hemoglobin and corpuscular concentration were calculated by the method already outlined. The technique of these blood determinations was exactly the same as that followed in the determination of blood values in normal young men[7] and women[8] and, since these methods have already been fully described and their accuracy analyzed, they need not be detailed again. It will suffice to say that for each determination two red cell counts were made, the results of these only accepted when they agreed within 100,000 cells per cubic millimeter, and the average of two such counts recorded; hemoglobin was determined by means of a Newcomer hemoglobinometer restandardized by the van Slyke method; and the volume of packed red cells was determined by means of a hematocrit devised by the writer.[18]

When occasion permitted the diameters of the red cells were measured. For this a Leitz micrometer eyepiece, calibrated by means of a slide micrometer for the tube length and lenses employed, was used. The diameter of all round cells coming under the scale of the micrometer was determined and at least 100 cells were measured in this way in each case. The cells were classed in groups progressing by 0.5 μ.

Mean corpuscular thickness was calculated from the mean corpuscular volume and mean cell diameter by the formula,

$$T = \frac{C.\,V.}{\pi\left(\frac{D}{2}\right)^2}$$

where T refers to thickness, C. V., mean corpuscular volume, and D, mean cell diameter. The red corpuscle is presumed to be a short

cylinder. It is obvious that mean corpuscular thickness can only be approximately estimated by this method.

The results of these determinations are presented in Tables I and II. Some of the patients were followed from the time of severe relapse to complete remission. Other patients could not be observed as long as might be desired because economic necessity or social convenience on the part of the patient, or the desire on the part of the attending physicians to keep patients in the wards for as brief a time as possible, necessitated their removal from the hospital and city. The remark that the administration of liver diet or extract is frequently followed by such rapid and satisfactory results in pernicious anemia and sprue that the patient is often unwilling to remain under observation for any length of time, is well borne out in some of these cases.

TABLE I.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN PERNICIOUS ANEMIA.

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, μ.	Mean cell thickness, μ.	Mean corpuscular volume, cu. μ.	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks.
80	1.28	8.49	1.84	104	37	36	Typical case; white male, 54 years.
	1.24	...	...	97	35	36	Liver diet and extract (ii vials t.i.d.) 4 days.
	1.45	...	...	135	39	29	" " 10 "
	1.93	8.91	2.14	133	39	30	" " 16 "
	2.72	...	...	105	33	31	" " 22 "
	3.21	...	...	106	32	30	" " 33 "
	3.78	...	...	100	32	32	" " 39 "
	4.07	8.24	1.70	90	28	30	" " 46 "
	4.69	...	...	87	28	32	Liver extract (ii vials t.i.d.) 67 "
	4.65	...	...	87	30	34	" " 81 "
	5.38	...	...	79	30	38	" " 109 "
94	1.88	...	...	97	34	35	Colored female, 48 years; marked neurologic symptoms and signs.
	2.22	8.41	1.87	104	33	32	Liver diet and extract (ii vials t.i.d.) 8 days.
	3.31	...	...	86	28	33	Changed to pellagra diet at 9 days; now 15 days.
	3.57	7.66	1.82	84	29	35	Pellagra diet 23 days.
	3.87	...	...	80	27	34	" 29 days.
	4.25	...	...	86	27	32	" liver extract (i vial daily) 35 days.
	3.82	...	...	88	28	32	" only; no extract for 1 week, 44 days.
	4.55	...	...	80	27	33	" (containing liver) 50 days.
93	3.18	...	...	111	34	31	White female, 26 years; disturbance chiefly neurologic.
	3.21	...	...	109	38	35	Liver extract (ii vials t.i.d.) 8 days.
	3.90	...	...	96	34	35	" 14 "
	3.93	...	...	100	35	35	" 21 "
	4.19	...	...	97	35	36	" 26 "
	4.48	...	...	89	32	36	" 36 "
	4.77	...	...	87	30	34	" (i vial daily) 50 "
	4.85	...	...	80	27	33	Ventriculin (4 cc. daily) 92 days.
9	1.42	8.70	2.51	130	41	32	Negro male, 51 years; symptoms chiefly cardiac.

TABLE I.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN PERNICIOUS ANEMIA. (*Continued.*)

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, μ.	Mean cell thickness, μ.	Mean corpuscular volume, cu. μ.	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks
	2.34	...	...	123	34	28	Liver diet 10 days.
	4.01	...	...	103	30	29	" 20 "
	4.20	8.26	1.67	90	26	29	" 31 "
	3.83	...	...	80	27	34	" 42 "
91	0.86	...	...	102	37	37	White female, 47 years; typical case.
	1.30	8.27	2.10	113	37	32	Liver extract (ii vials t.i.d.) Blaud's (gm. 1) 9 days.
	2.72	...	...	97	30	31	" " 16 "
	3.39	...	...	86	29	33	" " 22 " Discharged.
61	0.94	8.14	2.14	112	42	37	White male, 60 years; typical case.
	1.00	...	...	107	41	39	Liver extract (ii vials t.i.d.) 4 days.
	1.46	...	...	124	48	38	" 9 " Left hospital.
65	1.33	...	...	141	50	35	White male, 80 years; typical case.
	1.91	8.37	2.04	113	39	35	Liver extract (iii vials daily) 7 days. Discharged.
83	2.34	8.55	1.89	108	36	33	Negro male, 59 years, symptoms chiefly neurologic.
	2.63	...	...	102	32	31	Liver extract (i vial t.i.d.) 6 days.
	2.44	...	...	113	31	27	" 12 " Bronchopneumonia. Died 2 days later; autopsy confirmed diagnosis.
7	0.90	9.50	2.31	164	49	30	White male, 74 years; typical case.
	2.10	9.56	1.66	120	34	29	Liver diet 10 days; left hospital 4 days later.
17	1.46	8.70	1.71	101	34	34	White male, 66 years; typical case.
	1.33	...	...	110	38	34	Liver diet 6 days; reticulocytes, 18 per cent.
14	2.19	8.25	2.15	109	31	29	White female, 49 years, after 17 days liver diet.
1	4.03	...	...	96	32	33	White female, 33 years, has taken liver diet somewhat irregularly for 2 years.
122	0.93	8.62	1.96	114	43	38	White female, 56 years; typical case.
	1.18	...	...	118	37	32	Valentine extract, 30 cc. b.i.d.; liver diet; Blaud's, 1 gm. daily; 8 days.
	1.79	...	...	105	32	31	Valentine extract 30 cc. b.i.d. (and transfusion 200 cc.); 11 days.
	2.22	...	...	107	33	31	Extract, diet and iron, as above, 15 days.
	2.56	...	...	106	33	32	" " " " 18 "
	2.68	7.74	2.19	103	31	30	" " " " 22 "
	3.10	...	...	87	29	33	" " " " 25 "
	3.02	...	...	99	30	30	" " " " 29 "
	3.32	...	...	95	29	30	" " " " 34 "
124	1.18	8.93	2.31	146	45	30	White female, 61 years, symptoms chiefly gastrointestinal.
	1.37	...	...	140	44	31	Liver extract (ii vials t.i.d.) 3 days.
132	0.59	8.48	1.98	112	38	34	Negro male, 42 years; typical case; died (bronchopneumonia); diagnosis confirmed at autopsy.
135	1.28	8.29	1.94	105	36	34	White female, 62 years, relapsed because diet neglected;
	1.12	...	...	105	39	37	not taking extract.

All the patients suffering from pernicious anemia were treated by means of a liver diet, liver extract, or both. Unless otherwise

specified, liver diet consisted in the administration of a well-balanced diet which included 250 gm. of raw or lightly cooked liver daily. The liver extract used in the great majority of the cases was that prepared by Eli Lilly & Co. (No. 343). The administration of adequate quantities of liver or liver extract was followed by a

TABLE II.—SIZE AND HEMOGLOBIN CONTENT OF RED CORPUSCLES IN SPRUE.

Case No.	Red blood cells in millions per c.mm.	Mean cell diameter, μ.	Mean cell thickness, μ.	Mean corpuscular volume, cu. μ.	Mean corpuscular hemoglobin, micromicrograms.	Mean corpuscular concentration, per cent.	Remarks.
48	1.72	8.90	1.73	108	36	33	White male, 70 years, typical sprue.
	1.60	...	...	121	38	32	Liver diet and extract (iii vials daily) 4 days.
	1.46	9.76	1.77	132	40	30	" " " " 11 "
	2.04	...	...	134	38	28	" " " " 18 "
	2.69	...	...	118	31	26	" " " " 26 "
	3.06	...	...	117	30	26	" " " " 32 "
	3.12	8.99	1.89	121	34	28	" " " " 39 "
	3.75	...	...	104	34	33	" " " " 46 "
	4.15	...	...	99	31	31	" " " " 61 "
	5.06	8.38	1.51	83	29	35	Liver diet only 86 "
	4.68	...	...	94	32	34	" " 134 "
	5.28	8.13	1.79	93	31	33	Liver, 250 gm., 3 times a week 225 "
	5.32	...	...	88	29	33	" " " " 353 "
54	3.03	8.66	1.96	116	40	34	White male, 40 years, typical sprue.
	3.11	...	...	127	41	33	Liver extract (ii vials t.i.d.) 17 days.
	4.50	...	...	94	34	36	" " " 32 "
	5.52	...	...	82	29	35	Liver diet, 166 days.
	4.98	8.06	1.82	92	33	36	" 323 " (mild bronchitis at present).
73	0.62	...	...	160	58	38	White male, 63 years, typical sprue; given liver diet.
	5.43	...	...	78	28	36	Returned after 5 months for check-up.
	5.04	...	...	82	29	35	Blood reëxamined after 6 months.
108	2.16	...	...	132	46	35	White male, 43 years, typical sprue; had recovered 1 year ago from similar condition on liver diet but has discontinued treatment.
	2.11	9.16	1.82	120	40	33	Three days later; treatment not yet instituted.
	2.45	...	...	118	38	31	Raw pancreas (300 gm. daily) 1 day.
	2.52	...	...	131	41	32	" " 7 days.
	2.45	...	...	115	36	30	" " 12 " Developed bronchopneumonia and died.
4	4.09	8.64	1.68	98	32	32	White male, 36 years, sprue of moderate severity.
	3.72	8.27	1.91	102	27	27	"Sprue" (high-protein) diet 24 days.
	4.06	...	...	94	30	32	Sprue diet with liver 55 "
	4.43	8.04	1.87	96	32	33	Liver diet 69 " Discharged; improved.
53	2.64	...	...	114	35	33	White male, 48 years, typical sprue.
	3.24	...	...	115	39	36	"Sprue" (high-protein) diet 15 days.
	3.51	...	...	101	33	33	" " " 30 "
	3.07	...	...	114	39	34	" " " 75 " Discharged.
47	3.30	...	...	110	38	35	White male, 49 years; sprue, untreated.
136	3.05	9.33	1.75	117	35	33	White male, 37 years; typical sprue.

rapid and characteristic remission. A change from adequate to insufficient quantities of liver, as occurred in Case 94, was associated with a slowing up in the rate of recovery. Remission was also unfavorably influenced by the presence of infection (Case 83). As these phenomena have already been adequately commented upon in the literature, they will not be discussed here.

Three of the patients suffering from sprue were treated by means of liver diet and liver extract. The response in these patients was in every way similar to that observed in pernicious anemia. Another (Case 108), a man who had a year before been successfully treated for what was apparently the same condition by means of a liver diet but had suffered a relapse probably because he had taken no liver for nine months, was given 250 to 500 gm. of raw pancreas daily. The response, both as regards symptoms and blood, was not as marked as might have been expected to follow the administration of similar quantities of raw liver. Unfortunately the patient developed bronchopneumonia and died. An autopsy could not be obtained.

Two other patients suffering from sprue (Cases 4 and 53) were given "sprue diets" containing 55 gm. each of liver and pancreas daily. Although both were symptomatically somewhat improved, the blood indicated that comparatively little real improvement had taken place. When an adequate amount of liver was included in the diet of one of these patients (Case 4), definite improvement took place.

I. **The Volume and Thickness of the Red Corpuscle.** That corpuscular volume values sufficiently greater than normal to be of value in facilitating diagnosis are found in pernicious anemia, is suggested by the fact that, in 16 individuals first examined at various stages of the disease, mean corpuscular volume values ranging from 164 to 96 cu. μ and averaging 116 cu. μ were found. The red cell counts in these individuals ranged from 0.59 million to 4.03 million per cubic millimeter. Likewise in 8 patients suffering from sprue of all degrees of severity, as is indicated by their red cell counts which at first examination ranged between 0.62 million and 4.09 million per cubic millimeter, the corpuscular volume values ranged between 160 cu. μ and 98 cu. μ.

That the mean volume of the red cells in pernicious anemia and sprue is correlated to a marked degree with the red cell count, being as a general rule greater the lower the red cell count, is obvious from even a cursory examination of the values listed in Tables I, II and III. This relationship may be expressed mathematically by the correlation coefficient which for 100 blood examinations in the 16 cases of pernicious anemia and 8 cases of sprue is -0.6980 ± 0.0346. The correlation between mean corpuscular volume and number of red corpuscles is linear, since the correlation ratio is not significantly greater than the correlation coefficient (see Table IV) (see Pearl[9]).

TABLE III.—VALUES OF PHYSICAL CONSTANTS AT VARIOUS LEVELS OF RED CELL COUNT.

Number of red cells, millions per c.mm.	Number of cases.		Corpuscular volume, cu. μ.		Corpuscular hemoglobin, γγ.		Corpuscular concentration, per cent.	
	Pernicious anemia.	Sprue.	Pernicious anemia.	Sprue.	Pernicious anemia.	Sprue.	Pernicious anemia.	Sprue.
00 to 0.99 . . .	5	1	121	160	42	58	35	38
1.00 to 1.99 . . .	19	3	117	120	39	38	35	32
2.00 to 2.99 . . .	12	8	108	123	32	38	30	31
3.00 to 3.99 . . .	15	11	94	113	31	35	33	32
4.00 to 4.99 . . .	12	7	89	95	29	31	33	35
5.00 to 5.99 . . .	1	6	79	84	30	29	38	35

TABLE IV.—ZERO-ORDER CORRELATION COEFFICIENTS AND RATIOS.

Characters correlated.	Correlation coefficient.	Correlation ratio.	Corrected correlation ratio.	$\sqrt{K-1}/N = 0.67449/\sqrt{N}$.	$\zeta = \eta^2 - r^2$.
No. of R.B.C. and corp. vol. . .	−.6980 ± .0346	.7784	.7528	.3317 ± .0675	.1185 ± .0439
No. of R.B.C. and corp. hb. . .	−.6390 ± .0399	.7510	.7218	.3317 ± .0675	.1555 ± .0473
No. of R.B.C. and corp. conc. . .	+.0066 ± .0675	.4475	.3185	.3605 ± .0675	.1191 ± .0372
Corp. vol. and corp. hb.	+.8537 ± .0184	.8840	.8718	.3317 ± .0675	.0528 ± .0315
Corp. vol. and corp. conc. . . .	−.2276 ± .0521	.4464	.3200	.3605 ± .0675	.1474 ± .0449
Corp. hb. and corp. conc. . . .	+.2353 ± .0638	.4520	.3255	.3605 ± .0675	.1489 ± .0447

The usefulness of mean values for the size of red cells as an aid in differentiating the anemias has been questioned by some investigators because, they argue, unusually small as well as abnormally large red cells are found in such conditions as pernicious anemia and sprue. These investigators feel that the variations in the size of the cells may be such as to equalize one another and that in many instances no noteworthy average alterations in size from the normal may be noted. This objection is valid for mean cell diameter values. Thus Price-Jones[10] states that, "an excessive variability is even more constant in pernicious anemia than a high mean diameter," and he reports a number of values for mean diameter during the stages of relapse which certainly are not significantly greater than normal. However, in marked contrast to the uncertainness of mean diameter values, in all the cases of pernicious anemia and sprue examined by the writer during the stages of relapse, mean

corpuscular volume values significantly greater than normal have been found. Likewise Haden[1] reported an average volume of 128 cu. μ with values ranging from 163 to 108 cu. μ in 20 cases of pernicious anemia, and Gram[11] found in 10 cases values ranging from 136 to 94 cu. μ and averaging 117 cu. μ. In 8 cases Mills[12] reported values ranging between 135 and 95 cu. μ but in 2 other cases he found values below 95 cu. μ. In 1 of these patients a mean corpuscular volume of 90 cu. μ and a red cell count of 0.67 million were found, while in the other a mean volume of 88 cu. μ and a count of 3.06 million are reported.* Mills' lower values are partially accounted for by the fact that he apparently made no correction for the shrinkage in cell volume which results from the use of crystals of potassium oxalate as an anticoagulant.

The finding in pernicious anemia and sprue of mean corpuscular volume values greater than normal can be explained by the hypothesis that any alteration in the size of the red corpuscle occurs in all dimensions. As a consequence, any alteration in size which may be too slight to be considered significant when only one dimension, such as diameter, is measured, can be readily observed when a value which expresses alterations in all dimensions, is determined. By the measurement of corpuscular volume, variations in corpuscular thickness as well as in all diameters of the cell, are estimated.

Values for mean corpuscular thickness, estimated indirectly from mean corpuscular volumes and mean diameters in the manner already described, support this hypothesis. Gram[11] found an average cell thickness of 1.84 μ in 8 normal individuals, an increase in thickness in pernicious anemia and a decrease in the microcytic anemias. In 7 instances in which both mean corpuscular volumes and mean diameter were normal, I found values for mean thickness ranging from 1.53 μ to 1.78 μ and averaging 1.66 μ. In pernicious anemia and sprue the values were distinctly greater than this during the stages of relapse (Tables I, II). These values contradict Emmons'[13] statement that, "the pathologically enlarged cells that occur in pernicious anemia seem to undergo no increase in thickness." It may be here noted that Ponder's[14] measurements of the red cells of various mammals contradict Emmons' finding that the thickness of the red cells of different species of mammals is nearly the same in all cases.

In Chart I are shown the relative increases in mean corpuscular volume and mean diameter as found in 32 determinations in 14 cases of pernicious anemia and 5 cases of sprue. The increases in size have been calculated in each case in proportion to the mean normal corpuscular volume (82 cu. μ) and the mean diameter (7.9 μ) for this locality, and are expressed as per cent in proportion to these

* The values in cubic microns are derived from values reported by Haden and Mills in cubic centimeters $\times 10^{-11}$.

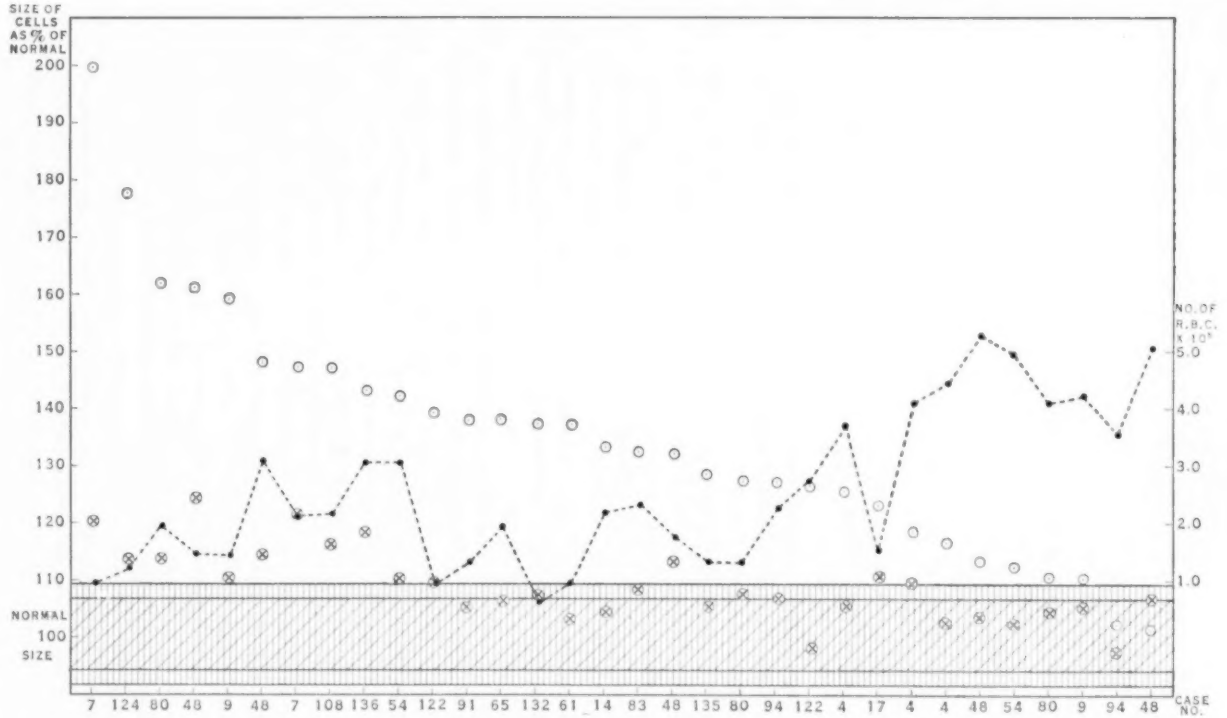

CHART I.—The comparative value of mean corpuscular volume determinations and mean cell diameter values in the diagnosis of macrocytosis. Thirty-two determinations in 14 cases of pernicious anemia and 5 cases of sprue in all stages of severity. The values for mean corpuscular volume and mean cell diameter are expressed as per cent of normal, 82 cu. μ being taken as the mean normal corpuscular volume, and 7.9μ the mean normal diameter. The corpuscular volume values have been arranged in order of magnitude and the corresponding cell diameter and red cell count are placed in the corresponding vertical position. ⊙ is the corpuscular volume, ⊕ the cell diameter, and ● the red cell count for each patient. The larger vertically shaded portion denotes the normal range of variation in corpuscular volume and the smaller diagonally shaded area the normal range of cell diameter as indicated by the coefficients of variation for these values, 9 per cent and 6.3 per cent respectively.

normal values. This figure illustrates graphically the opinion already expressed, namely, that the deviations of mean corpuscular volume from normal are very great during the severe stages of pernicious anemia and sprue when the red cell count is low, whereas values for mean diameter are increased only to a small and frequently insignificant degree.

TABLE V.—MEAN VALUES FOR CORPUSCULAR DIAMETER, THICKNESS AND VOLUME IN PERNICIOUS ANEMIA AND SPRUE.

Red cell count, millions per c.mm.	Number of determinations.	Mean diameter, μ.	Mean thickness μ.	Mean volume, cu. μ.
0 to 0.99	4	8.69	2.10	126
1.00 to 1.99	10	8.73	2.01	119
2.00 to 2.99	6	8.63	1.93	111
3.00 to 3.99	5	8.58	1.87	108
4.00 to 4.99	5	8.25	1.75	93
5.00 to 5.99	2	8.25	1.65	88

Discussion. The results presented in this paper clearly indicate, I believe, that the calculation of mean corpuscular volume offers for the detection of macrocytosis a method which is both simple and reliable. It is obviously essential that accuracy be observed in the determination of the red cell count and the volume of packed red cells from which corpuscular volume is calculated. When reasonable care is observed, both these determinations can be made with relatively great precision. In the past much reliance has been placed in the diagnosis of pernicious anemia on the relative amounts of hemoglobin and red cells (color index). It has frequently been pointed out that the generally employed methods of hemoglobin estimation are very inaccurate and unreliable. The volume of packed red cells, on the other hand, can be determined with very much greater accuracy.[8] It follows that, as long as methods of hemoglobin determination remain as inaccurate as they now are, a method for the detection of macrocytosis which depends on volume determination is of particular value.

As compared with cell diameter measurements, corpuscular volume determinations are simple and, since variations in volume depend on alterations in all dimensions, they are more useful in detecting average variations in the size of the red cell. It is true that this method affords no conception of the variation in the size of the cells of a single sample. Such information is undoubtedly very valuable and when it is necessary to have exact knowledge in this respect the calculation of corpuscular volume certainly cannot replace the measurement of the diameters of a large number of cells. Information concerning variation more exact than can be gained by a few minutes' examination of a stained smear is, however, rarely necessary in clinical work. In the great majority of instances, the calculation of corpuscular volume can take the place of a time-consuming and tedious laboratory procedure.

Two questions concerning corpuscular volume that now arise may be stated as follows:

1. Are values for corpuscular volume greater than 95 cu. μ found only in pernicious anemia or sprue?

2. Can any differences between these two diseases be detected with the aid of corpuscular volume determinations?

The latter question is readily answered. In so far as can be concluded on the basis of the small number of cases here observed, no differences between these two diseases in respect to the mean volume of the cells have been noted. In reply to the first question it may be said that, in the course of some 400 or more similar blood examinations in 140 patients suffering from a large variety of diseases, corpuscular volume values of 95 cu. μ or more have been repeatedly found, in addition to the 24 cases of pernicious anemia and sprue here presented, in only 7 individuals. In 3 of these patients the diagnosis of pernicious anemia or sprue suggested itself because of the symptoms and signs but a final diagnosis which fulfilled the criteria already mentioned could not be made, in 1 case because of lack of coöperation on the part of the patient, and in the other 2 because the response to liver therapy was indefinite. In one of these the presence of a low-grade erysipeloid infection of the leg was probably responsible for the inadequate response to liver therapy since the blood picture returned to normal as the infection cleared up and liver therapy was continued. Two other patients were suffering from syphilis of the gastrointestinal tract. Another patient, a woman in the sixth month of pregnancy, presented an anemia of the "pernicious" type. The last patient was a man whose blood was examined a few hours after a large hemorrhage from a gastric ulcer. The subject of macrocytosis in conditions other than pernicious anemia or sprue will be considered in detail when more material has been gathered. The present material suggests that values for corpuscular volume greater than normal are rarely found in other than these two diseases and, when found, differentiation is usually readily made on the basis of the other findings. Very high values have been observed only in pernicious anemia and sprue. In the 4 cases mentioned above as probably being neither pernicious anemia or sprue the highest corpuscular volume observed was 116 cu. μ, while the majority of the values ranged between 95 and 105 cu. μ.

II. **The Hemoglobin Content of the Red Corpuscle.** Like the values for mean corpuscular volume, abnormally high values for mean corpuscular hemoglobin were found in the stages of relapse of pernicious anemia and sprue. That these were sufficiently greater than normal to be significant in diagnosis is indicated by the fact that, at the first examination of the 16 patients suffering from pernicious anemia, values for corpuscular hemoglobin ranging from 50 to 31 $\gamma\gamma$ and averaging 39 $\gamma\gamma$ were found. Likewise in the 8 sprue

patients values ranging from 58 to 32 $\gamma\gamma$ and averaging 40 $\gamma\gamma$ were found. The results of the blood examinations are presented in detail in Tables I and II.

The values for mean corpuscular hemoglobin were on the whole highly correlated with the red cell count. The sign of correlation was negative; that is, the lower the cell count, the greater were the values for mean corpuscular hemoglobin. The coefficient of correlation between these two characters was -0.6390 ± 0.0399, which is slightly less than that for number of red cells and corpuscular volume. Considering probable errors, however, this difference can scarcely be considered significant. Although the correlation ratio is greater than the correlation coefficient and $\zeta = \eta^2 - r^2$ is somewhat more than three times its probable error, since this value does not take account of the effect of the number of arrays on the value of the correlation ratio, it can be concluded that probably the correlation of corpuscular hemoglobin and number of red cells is linear.[9] The mean values found at various levels of the red cell count in pernicious anemia and sprue are shown in Table III.

In comparison with the variations in the values for corpuscular volume and corpuscular hemoglobin, the values for corpuscular concentration showed relatively little fluctuation. Thus, at the first examination of the 16 cases of pernicious anemia corpuscular concentration values ranging from 29 to 37 per cent and averaging 34 per cent were found, and in the 8 sprue patients these values ranged from 32 to 38 per cent, also averaging 34 per cent. Again, in marked contrast to the high degree of correlation between number of red cells and corpuscular volume or corpuscular hemoglobin, is the striking lack of correlation between number of red cells and corpuscular concentration. This is clearly evident from inspection of Tables I, II and III, and is indicated by the coefficient of correlation between these two variables, $+0.0066 \pm 0.0675$, which is less than its probable error. Although the correlation ratio for these two characters is high (Table IV) this ratio when corrected for the influence of number of arrays is less than $\sqrt{(\kappa - 1)/N}$, which is the mean value of the correlation ratio in samples from an uncorrelated population (see Pearl[9]).

The correlation between corpuscular concentration and corpuscular volume and corpuscular hemoglobin, respectively, is indicated by the values presented in Table IV. The coefficient of correlation for corpuscular volume and corpuscular concentration is more than 4 times its probable error and is therefore significant. The sign of correlation is negative and the coefficient is small. This means that, judging by the material here presented, the concentration of hemoglobin in the red corpuscle is to a small extent inversely related to the volume of the corpuscles in pernicious anemia and sprue. It will be noted that the correlation ratio, when corrected for the influence of number of arrays, is less than the mean correlation ratio

for a totally uncorrelated population. The correlation coefficient for corpuscular concentration and corpuscular hemoglobin is likewise small but the sign of correlation is positive. This indicates that corpuscular concentration values tend to be higher as corpuscular hemoglobin values become greater. Again the corrected correlation ratio indicates no significant association between these variables. On the whole, then, it may be said that no well-defined relationship appears to exist between corpuscular concentration and either corpuscular volume or corpuscular hemoglobin.

In marked contrast to this lack of significant correlation is the high value for the coefficient of correlation between corpuscular volume and corpuscular hemoglobin ($+0.8537 \pm 0.0184$). The corrected correlation ratio is also high (Table IV) and is significantly greater than $\sqrt{(\kappa-1)/N}$, but $\zeta = \eta^2 - r^2$ is scarcely greater than its probable error, which means that the correlation between corpuscular volume and corpuscular hemoglobin is linear.

The mean, median, standard deviation and coefficient of variation for number of red corpuscles, corpuscular volume, corpuscular hemoglobin and corpuscular concentration of the 100 pernicious anemia and sprue blood samples are shown in Table VI where they are compared with the variation constants for 100 young men, nineteen to thirty years of age, previously reported by me.[15] The values for healthy young men may, for the purpose of this comparison, serve as an index of the normal although the patients studied were unselected as regards sex or age. Most striking in the comparison of the values presented in the table are the great differences in the variation constants for number of red corpuscles, corpuscular volume and corpuscular hemoglobin in health and disease, as compared with the similarity in the values for corpuscular concentration. Considering probable errors, it may be said that the mean, median, standard deviation and coefficient of variation for corpuscular concentration in the 100 healthy young men and in the cases of pernicious anemia and sprue are equal.

Discussion. Two conclusions stand out quite clearly in the analysis of the data here presented. The first of these is concerned with the high degree of correlation between the size of erythrocytes in pernicious anemia and sprue and the amount of hemoglobin they contain (corpuscular hemoglobin). Variations in corpuscular volume are on the whole accurately paralleled by variations in corpuscular hemoglobin, increases in size being associated with similar, although sometimes somewhat less marked, increases in hemoglobin content. The coefficient of correlation between corpuscular volume and corpuscular hemoglobin is very high. A similar parallelism between variations in these two characters has been noted not only in the 7 cases of macrocytic anemia already mentioned as not being definitely diagnosed as pernicious anemia or sprue or definitely known to be due to other causes, but has been noted as well in a large number of anemias of other types.[16]

TABLE VI.—VARIATION CONSTANTS IN 100 HEALTHY MALES AND IN 100 DETERMINATIONS IN PERNICIOUS ANEMIA AND SPRUE COMPARED.

Variation constants.	Mean.	Median.	Standard deviation.	Coefficient of variation.
Number of red corpuscles $\times 10^6$:				
100 healthy males	5.854 ± 0.037	5.770 ± 0.046	0.548 ± .026	9.36% ± 0.43
Pernicious anemia and sprue	2.955 ± 0.199	3.063 ± 0.250	1.354 ± .065	45.82% ± 2.6
Corpuscle volume, cu. μ:				
100 healthy males	79.9 ± 0.5	80.6 ± 0.6	7.2 ± .3	9.06% ± 0.43
Pernicious anemia and sprue	106.6 ± 7.2	104.9 ± 9.0	17.0 ± .8	15.94% ± 0.78
Corpuscular hemoglobin, $\gamma\gamma$:				
100 healthy males	27.38 ± 0.17	28.09 ± 0.21	2.51 ± .12	9.18% ± 0.43
Pernicious anemia and sprue	35.02 ± 2.37	34.17 ± 2.98	5.90 ± .28	16.00% ± 0.78
Corpuscular concentration, per cent:				
100 healthy males	34.4 ± 0.2	34.0 ± 0.3	2.96 ± .14	8.60% ± 0.43
Pernicious anemia and sprue	33.3 ± 2.2	33.4 ± 2.7	2.78 ± .13	8.33% ± 0.38

The second observation is concerned with the values for corpuscular concentration. The remarkable lack of correlation between corpuscular concentration and the other variables here considered, and the relative lack of variation in this character generally, is worthy of speculation. As will be seen from inspection of the data presented in Tables I, II, III and VI, the values for corpuscular concentration remained on the whole remarkably well within the range of variation noted in normal individuals. It is noteworthy that none of the values are greater than those which have been observed in normal individuals and therefore bear out the contention that, at least as far as can be determined by present methods, the red corpuscle does not become "supersaturated" with hemoglobin in pernicious anemia or sprue. Again, few of the values for corpuscular concentration were lower than normal. These low values will be discussed again later. On the whole it may be said that the changes in the red corpuscles in these cases of pernicious anemia and sprue were in the nature of increases or decreases in size with generally parallel changes in the amount of hemoglobin contained in the cells and a remarkable constancy in the values for corpuscular concentration.

Work in progress at the present time suggests that generally in the anemias significant alterations in the red corpuscles are in the nature of changes in size with parallel alterations in their hemoglobin content and a remarkable constancy in their concentration of hemoglobin. From the observations so far made it appears that this tendency to constancy in corpuscular concentration is only disturbed when there is a constant drain on the hemoglobin of the body as occurs in chronic hemorrhagic anemia.[16]

Regression Equations. From the correlation coefficients presented the following regression equations have been derived:

Mean corpuscular volume = 132.6 − (8.8 × number of red corpuscles).

Mean corpuscular hemoglobin = 43.3 − (2.8 × number of red corpuscles).

Mean corpuscular concentration = 33.2 + (0.01 × number of red corpuscles).

TABLE VII.—CORPUSCULAR CONSTANTS CALCULATED FROM REGRESSION EQUATIONS COMPARED WITH OBSERVED CONSTANTS (CASE 80).

Number of red cells, × 10^6.	Corpuscular volume, cu. μ.		Corpuscular hemoglobin, γγ.		Corpuscular concentration, per cent.	
	Calculated.	Observed.	Calculated.	Observed.	Calculated.	Observed.
1.28	121	104	40	37	33	36
1.24	222	97	40	35	33	36
1.45	120	135	39	39	33	29
1.93	116	133	39	39	33	30
2.72	109	105	36	33	33	31
3.21	104	106	34	32	33	30
3.78	99	100	33	32	33	32
4.07	97	90	32	28	33	30
4.69	91	87	30	28	33	32
4.65	92	87	30	30	33	34
5.38	85	79	28	30	33	38

In Table VII the corpuscular constants observed in one of the patients suffering from pernicious anemia (Case 80) are compared with the values for these constants calculated from these regression equations. It will be seen that the observed and calculated values for corpuscular volume and corpuscular hemoglobin agree remarkably well except during the severe stages of anemia. On the other hand, there is no parallelism whatever between the fluctuations in corpuscular concentration and the calculated values for this variable. This table illustrates in concrete form the remarkable correlation between the red cell count, and therefore the degree of anemia, and the volume and hemoglobin content of the red corpuscles in pernicious anemia and sprue and the apparently total lack of relation between the cell count and the concentration of hemoglobin in the red corpuscle.

The lack of agreement in the first four calculated and observed values for corpuscular volume in Table VII is interesting and important. Chart II is a scatter-diagram illustrating the correlation between number of red cells and mean corpuscular volume in all the cases of pernicious anemia and sprue. There is obviously much more scatter below the level of 2,000,000 red cells than there is above this value and on the whole it appears that there is much more correlation between corpuscular volumes and red cell counts at higher levels of the cell count than there is at low levels. The relative lack of

correlation in these values in the severe stages of anemia probably reflects the marked anisocytosis at this time, a factor which gradually disappears as the anemia becomes less severe. It is noteworthy that in none of these instances was the presence of small and distorted cells in the blood sufficient to reduce the values for mean corpuscular volume below 95 cu. μ during stages of moderate or severe anemia.

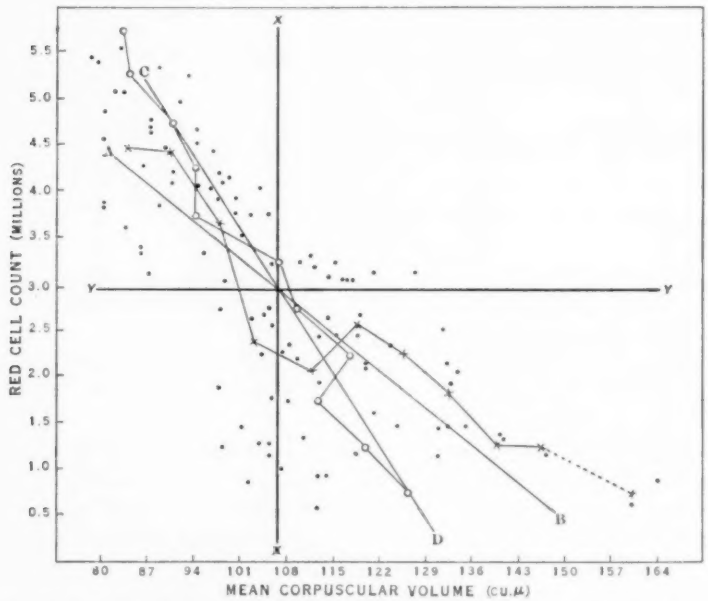

CHART II.—Correlation of mean corpuscular volume and red cell count in pernicious anemia and sprue. The black dots are the individual observations. The crosses are the means of the observed red cell arrays (observed regression of red cell count on corpuscular volume). *AB* is the calculated regression of red cell count on corpuscular volume. The circles are the means of the observed corpuscular volume arrays (observed regression of corpuscular volume on red cell count). *CD* is the corresponding calculated regression line. $\times\times$ gives the location on the corpuscular volume scale of the mean of all the 100 corpuscular volumes. *YY* gives the location on the red cell count scale of all the 100 cell counts.

III. **The Influence of Liver Therapy on the Volume and Hemoglobin Content of the Red Corpuscle.** The variations in the volume and hemoglobin content of the red corpuscle associated with the remissions induced by liver therapy in typical cases of pernicious anemia and sprue are illustrated by Charts III and IV. Alterations in number of red cells, average cell diameter, and mean corpuscular volume, corpuscular hemoglobin, and corpuscular concentration are measured in proportion to the normal mean values for each of these characters, all variations being expressed as per cent of normal.

The decrease in the size and hemoglobin content of the red cells as improvement takes place and the striking relationship between these characters and the red cell count, so characteristic of all the cases of pernicious anemia and sprue, are clearly demonstrated.

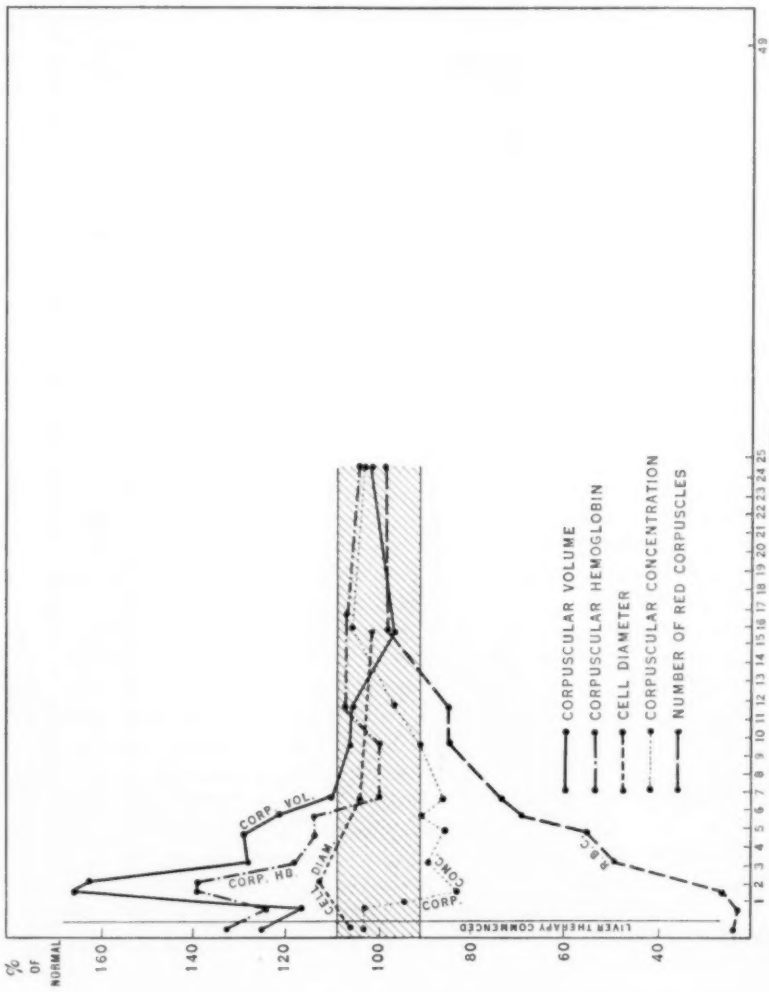

CHART III.—Variations in corpuscular constants associated with liver-induced remission in a case of pernicious anemia (Case 80).
Shaded area: Normal range of variation in all characters above mentioned except cell diameter, as measured by coefficient of variation.

The preliminary increase in the mean size and hemoglobin content of the red corpuscle preceding the later decrease in these values, shown in Charts III and IV, was noted in 6 of 8 cases of pernicious anemia and sprue in which a sufficient number of determinations was made for such observations to be possible. Although in one

of these cases the increase in mean corpuscular volume coincided with a slight preliminary fall in the red cell count during the first few days of liver therapy, in 5 of the 8 cases the increase in size occurred in spite of a rising cell count. Unfortunately reticulocyte counts were made at frequently repeated intervals in only 2 cases.

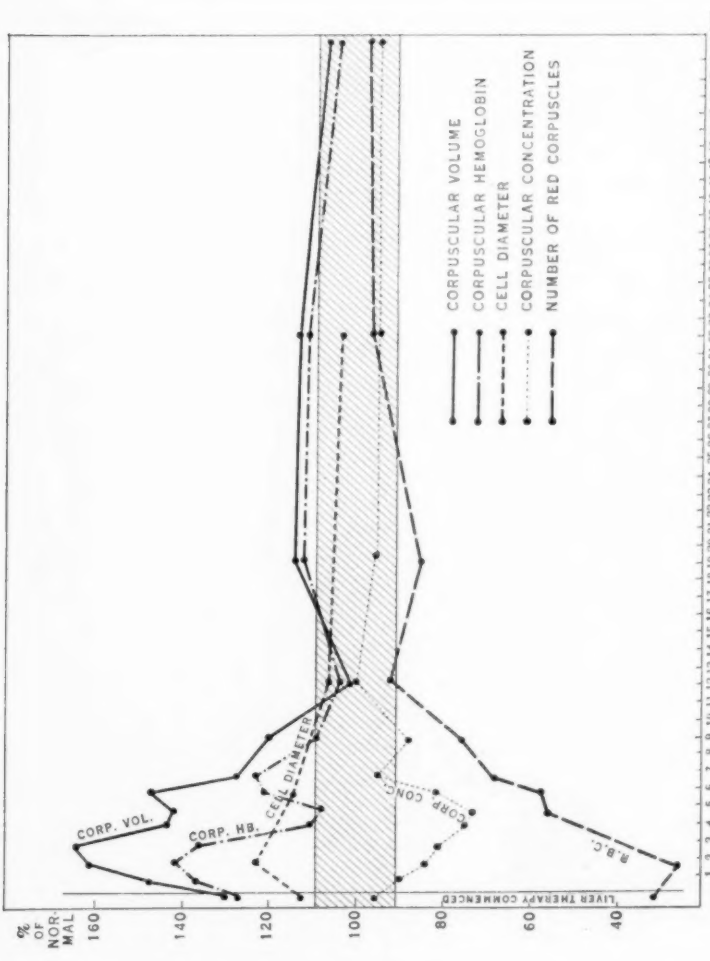
CORPUSCULAR VOLUME
CORPUSCULAR HEMOGLOBIN
CELL DIAMETER
CORPUSCULAR CONCENTRATION
NUMBER OF RED CORPUSCLES
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 WEEKS
CORP. VOL.
CORP. HB.
CELL DIAMETER
CORP. CONC.
R.B.C.
LIVER THERAPY COMMENCED
% OF NORMAL
160
140
120
100
80
60
40

CHART IV.—Variations in corpuscular constants associated with liver-induced remission in a case of sprue (Case 48).
Shaded area: Normal range of variation in all characters above mentioned except cell diameter, as measured by coefficient of variation.

In these cases the peak of the reticulocyte curve coincided with the maximum value for mean corpuscular volume. The data at hand are insufficient to draw any conclusions concerning the cause of this preliminary increase in corpuscular volume, but the recent report by Persons[17] that the reticulocytes in pernicious anemia are distinctly larger than the adult blood cells suggests that the association

of maximum corpuscular volume values with the peak of the reticulocyte curve in these cases may have been causal rather than coincidental. The disappearance of small poikilocytes from the blood stream as improvement takes place may also be a factor in this rise.

The variations in corpuscular concentration are of interest. It will be seen from inspection of Charts III and IV that there was a definite decrease in the values for corpuscular concentration during the early stages of liver therapy. This decrease occurred at the time when the increase in the number of red corpuscles and the changes in their size were taking place most rapidly. In 5 of 6 cases of pernicious anemia and sprue first examined at a time of severe relapse, as indicated by the low red cell counts, a similar marked reduction in the values for corpuscular concentration following liver therapy was observed. It is noteworthy that the response to liver therapy is most rapid and most marked in just such cases. On the other hand, in 2 patients first examined at a time when the red cell count was relatively high, no such reduction in corpuscular concentration following liver therapy took place. This suggests that in the stages of severe relapse the response to appropriate therapy is so sudden and rapid that either the newly-formed cells are produced so rapidly that they are filled with inadequate amounts of hemoglobin, or the supply of pigment in the body is soon exhausted by the rapid blood regeneration. Although it is well known that large pigment deposits are present in the liver, spleen, kidney and other organs in the stages of relapse it is not known whether this pigment may be mobilized rapidly or is present in sufficient quantity to meet with the requirements of unusually active blood regeneration. These findings suggest that the administration of iron along with liver therapy in pernicious anemia and sprue may have a rational basis. Two patients (Cases 91 and 122) who were given Blaud's pill, 1 gm. daily, in addition to the liver therapy, did not show as marked a reduction in corpuscular concentration values as was noted in those to whom no inorganic iron was administered. In all the cases in which a marked reduction in corpuscular concentration took place in the early stages of liver therapy, these values returned to normal at the time when blood regeneration became less rapid.

Summary and Conclusions. A series of 100 blood examinations has been carried out in 16 cases of pernicious anemia and 8 cases of sprue, of all degrees of severity and at varying intervals during remissions induced by liver therapy. Mean corpuscular volume, corpuscular hemoglobin, and corpuscular concentration were determined at each examination and in 32 instances cell diameter and mean corpuscular thickness were measured as well. As a result of these determinations the following conclusions seem justified.

1. The mean volume (mean corpuscular volume) and the hemo-

globin content (mean corpuscular hemoglobin) of the red corpuscles in pernicious anemia and sprue are significantly greater than normal during the stages of relapse of these diseases. The deviations of these values from the normal are of such magnitude and occur so constantly that they afford a simple and readily available aid in diagnosis and are useful in observing the alterations in the size and hemoglobin content of the red corpuscle which are associated with remission and relapse in these diseases.

2. Increases in mean corpuscular volume are of much greater magnitude than corresponding increases in average cell diameter and therefore the determination of mean corpuscular volume offers the more useful means of estimating variations in the mean size of the red cells. Even during the period of severe anemia at a time when numerous small and distorted cells are to be found in the blood, corpuscular volume values which were significantly greater than normal were constantly found. The greater value of mean corpuscular volume as compared with mean cell diameter determinations is explained by the fact that increases in the size of red corpuscles in all dimensions are observed when the mean corpuscular volume is calculated.

3. Both mean corpuscular volume and mean corpuscular hemoglobin are highly correlated with the red cell count in pernicious anemia and sprue. The correlation is linear and the sign of correlation is negative; that is, high values for these constants are found when the cell count is low and lower values are observed as the cell count rises. The correlation between mean corpuscular volume and the cell count is less marked in the severe stages of anemia than when the anemia is less marked (red cell count above 2 million), probably because of the presence of large numbers of small and distorted cells in the blood stream at such a time.

4. The upper limit of normal mean corpuscular volume has been arbitrarily fixed at 95 cu. μ. Higher values than this have rarely been found in conditions other than pernicious anemia or sprue.

5. In marked contrast to the values for corpuscular volume and corpuscular hemoglobin the concentration of hemoglobin in the red corpuscles showed no correlation whatever with the red cell count. Neither was there noteworthy correlation between corpuscular concentration and either corpuscular volume or corpuscular hemoglobin. The variations in corpuscular concentration were small in extent and of little greater magnitude than has been observed in normal individuals.

6. Abnormally high values for corpuscular concentration were not found at any time in the cases of pernicious anemia and sprue and no support has been found for the frequently repeated statement that the red corpuscles are supersaturated with hemoglobin in these diseases.

7. Low values for corpuscular concentration were found only at

the time of unusually active blood regeneration. The significance of this observation both as regards the pigment metabolism and the treatment of pernicious anemia and sprue, is briefly discussed.

8. Mean corpuscular volume and mean corpuscular hemoglobin were highly correlated with each other. It appears that a significant change in the blood in pernicious anemia and sprue is an increase in the mean volume and hemoglobin content of the red corpuscles. The increases in volume and in hemoglobin content tend, on the whole, to be parallel, with the result that the concentration of hemoglobin in the corpuscles is not significantly altered except under unusual circumstances.

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HUMAN ELLIPTICAL ERYTHROCYTES.

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Variations in the shape of the human red blood cells have been recognized for a long time. In most instances such variations show considerable diversity and are associated with anemia, either of the primary or of the secondary type. In such conditions the deformity in shape is considered generally as one of the forms of manifestations of the anemic process. However, there are two recognized clinical conditions in which the poikilocytosis is of one definite type, is hereditary, and is not dependent upon any anemia which may be present. One of these conditions, so-called sickle-cell anemia, is well established in the literature. The red blood cells in this condition are oval, elliptical and sickle-shaped. The sickle cells typically have long spinelike processes at their ends. The second example of an hereditary deformity in the red blood cells is much less well known and has no definite name. It is characterized by the presence of elliptical and oval erythrocytes in the peripheral blood of otherwise normal individuals. It occurs in both white and colored subjects. The first report of this latter condition was made by Dresbach.[3] Since this time, several additional reports have been made.[1, 2, 5, 7, 8, 9, 10, 12] During the past year 3 patients representative of this condition have been seen in the medical clinics of the Strong Memorial and Rochester Municipal Hospitals. It is the purpose of this paper to report the important data obtained from each of these subjects. All negative and irrelevant data are omitted in these reports.

Case Reports. Case I.—A. W., Unit No. 13082, an unmarried colored woman, aged forty-seven years, was admitted to the Rochester Municipal Hospital on June 7, 1930. She had active advanced pulmonary tuberculosis as evidenced by the history, the physical signs, the roentgenographic studies and an acid-fast strain of a smear of the sputum. She had been in this hospital twenty-eight months prior to her final admission with acute genitourinary symptoms associated with acute pyelitis and cystitis.

Laboratory Examinations. At the time of her first entry, her red blood cell count was 4,680,000 per c.mm. and her hemoglobin was 85 per cent (Sahli). At that time her red blood cells, in Hayem's solution and in a fixed smear stained with Wright's stain, showed a marked tendency toward oval forms. At her last entry, the red blood cell count was 3,590,000 per c.mm. The hemoglobin was 55 per cent (Sahli). The white blood cell count was 13,200 per c.mm. The differential count of a smear stained with Wright's stain was: neutrophils, 85 per cent; lymphocytes, 5 per cent;

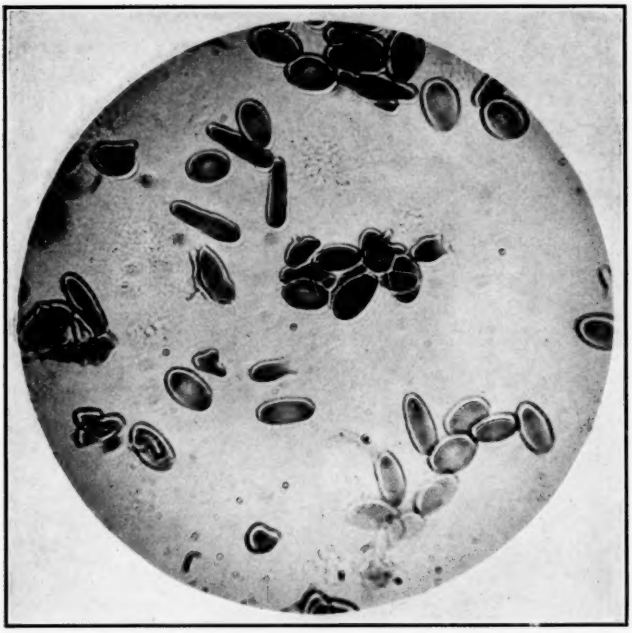

FIG. 1.—Microphotograph of an unstained sealed preparation of blood from Case I, A. W., at the end of one and a quarter hours.

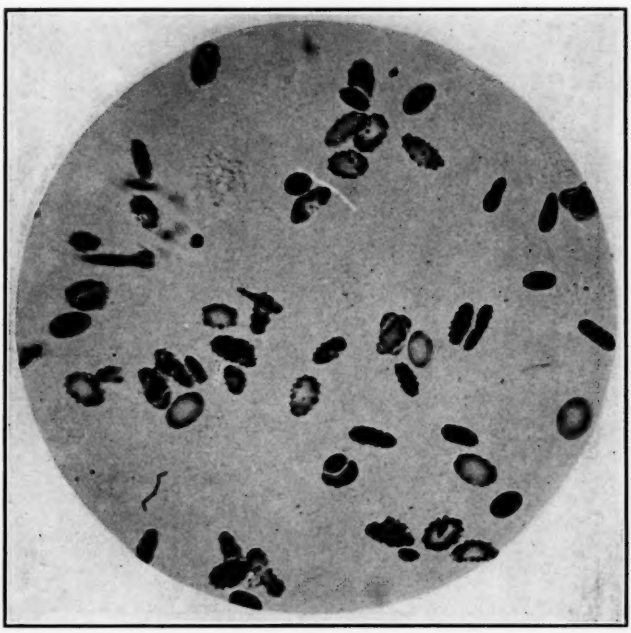

FIG. 2.—Microphotograph of an unstained sealed preparation of blood from Case I, A. W., at the end of twenty-four hours.

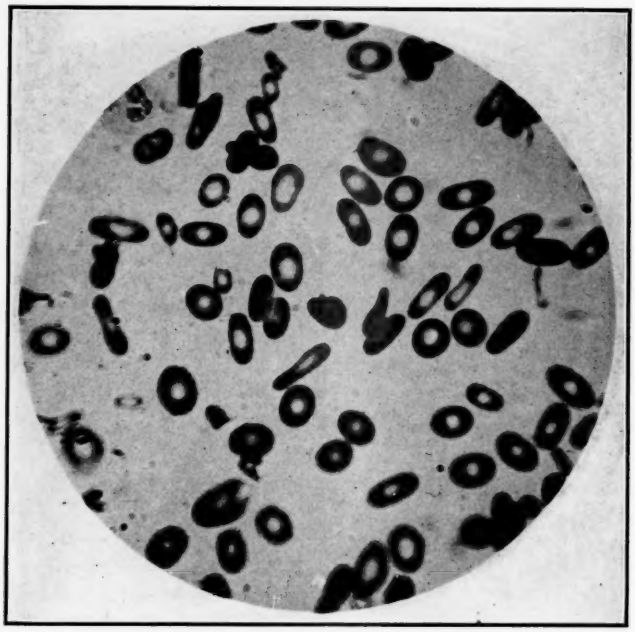

FIG. 3.—Microphotograph of a stained smear of blood from Case I, A. W.

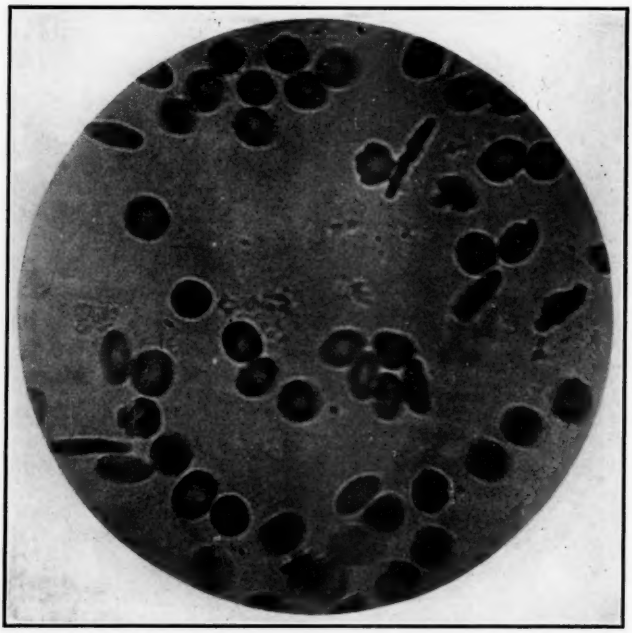

FIG. 4.—Microphotograph of an unstained sealed preparation of blood from Case II, B. M., at the end of thirty minutes.

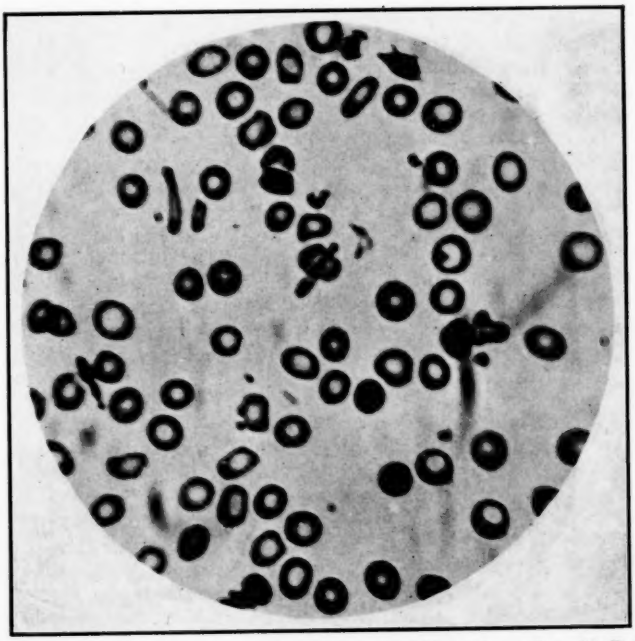

FIG. 5.—Microphotograph of a stained smear of blood from Case II, B. M.

monocytes, 7 per cent; degenerated cells, 3 per cent. The reticulocyte count was 1 per cent. It was noted that the red blood cells in the counting chamber in Hayem's solution were markedly irregular, there being a large percentage of sausage-shaped cells. Accordingly, a fresh unstained preparation sealed with vaselin was examined. The red blood cells were practically all distorted in shape, over 90 per cent of the cells being either oval or elliptical in shape. All gradations between slightly oval and typical long narrow sausage forms were seen. The longest cells averaged about twice the diameter of a normal red blood cell and were about one-fifth as wide as long. The cells had blunt, rounded ends. A few scattered cells had very fine threadlike filamentous processes. No typical sickle cells were seen. There were a few microcytes but no macrocytes. There was no evidence of phagocytosis of the red blood cells. The preparation was saved and examined twenty-four hours later. There was no increase in the sickling phenomenon, the red blood cells showing the same morphologic changes as when first examined except that mild crenation had occurred. A fixed smear stained with Wright's stain revealed the same type of poikilocytosis of the red blood cells as was seen in the fresh preparation. Repeated observations on fresh preparations revealed the same morphologic peculiarities of the red blood cells as were seen in the first preparation. Figs. 1, 2 and 3 show typical areas from fresh and fixed preparations of this patient's blood. A suspension of the patient's blood was made in a normal saline solution which contained 1.5 per cent of sodium citrate. One drop of this was put in a small chamber through which carbon dioxid was passed for twenty minutes, as described by Hahn and Gillespie.[6] There was no change in the morphology of the red blood cells. This procedure was repeated with the same results. The bleeding time was one and a half minutes and the coagulation time six minutes. The clot retracted normally and was firm and elastic. There were no other abnormal laboratory findings of any note.

Case II.—B. M., Unit No. 31110, a Russian Hebrew laborer, aged sixty-four years, was admitted to the Rochester Municipal Hospital January 2, 1930, with the chief complaint of "fainting spells." These attacks began two years before admission to the hospital and followed an injury to the left temporal region. The physical examination revealed no findings of interest other than pallor of the nail beds, the mucous membranes and the skin. Roentgenographic studies showed no abnormalities of interest.

Laboratory Examinations. The red blood cell count was 3,950,000 per c.mm. The hemoglobin was 45 per cent (Sahli). The white blood cell count was 6500 per c.mm. A differential blood count was normal. The particular findings of interest related to the morphology of the red blood cells, and the poikilocytosis was of the same type as that reported for Case I. The number of abnormally-shaped cells was less than in Case I, the average number of typical sausage-shaped cells being 3 or 4 per oil-immersion field. The elliptical red blood cells tended to be slightly longer than those seen in the blood of Case I and, in addition, typical sickle cells were seen at rare intervals. Five typical sickle cells were seen in one fresh preparation of the patient's blood. Repeated observations gave essentially the same findings. Fig. 4 shows a typical field in a fresh-sealed preparation. The Hahn and Gillespie[6] test and observations for latent sickling were negative. There were no other noteworthy abnormal laboratory findings.

Unstained specimens of blood from 4 children and 4 grandchildren of the patient were examined. Only 1 of the children of the patient showed the same morphologic peculiarities of the red blood cells as the patient. This person was a girl, aged twenty-four years. Her red blood cell count was 4,390,000 per c.mm. The hemoglobin was 80 per cent (Sahli). The

white blood cell count was 6900 per c.mm. One of the 4 grandchildren, whose blood was examined, showed a few oval red blood cells, but the changes were so slight that this subject could not be said to have the condition described as occurring in the patient. The other 3 grandchildren had red blood cells which appeared entirely normal.

CASE III.—L. A. B., Unit No. 27735, a white married woman, aged thirty-five years, entered the Rochester Municipal Hospital on March 20, 1930, on account of pain in her back of five days' duration. She had a past history suggestive of pulmonary tuberculosis which had been active eleven years prior to admission but had later become quiescent. No symptoms of activity of the pulmonary lesion had recurred until three months before her admission to the hospital, when she began to tire easily. Physical examination and Roentgen ray films of the chest revealed signs consistent with old pulmonary tuberculosis. An appendectomy was performed soon after admission to the hospital. Microscopic study of a section of the appendix showed findings which were diagnosed as "tuberculous and chronic appendicitis."

Laboratory Examinations. These were of interest only in regard to the blood. The red blood cell count was 4,690,000 per c.mm. The hemoglobin was 65 per cent (Sahli). The white blood cell count was 11,800 per c.mm. A differential count made on a smear stained with Wright's stain gave the following findings: Neutrophils, 91 per cent; lymphocytes, 4 per cent; monocytes, 5 per cent. There were 0.8 per cent of reticulocytes. The red blood cells, both in fixed and fresh preparations, on repeated observations presented essentially the same morphologic changes as those described for Case II, B. M. The blood of none of the relatives of this patient could be obtained for examination.

Discussion. An analysis of the data from each of the 3 patients shows that the symptomatology could be ascribed to some organic disease and not to the poikilocytosis of the red blood cells. In other words, there was found in these patients no symptomatology which could be properly explained by the presence of elliptical and oval red blood cells in the peripheral blood. This, of course, is what was to have been expected, since it has been well shown that these cells occur as a result of a congenital defect in blood formation and may be found in otherwise normal individuals. In his original description of the first subject known to have this blood picture, Dresbach[3] suggested that it was a congenital or developmental anomaly. He was unable to prove that the condition was actually transmitted as an hereditary characteristic as the only member of the subjects' family that was examined had normal red blood cells. However, later studies of this disorder by other investigators,[1, 7, 8, 9, 13] have shown that Dresbach's suspicion of an hereditary factor was correct. This conception is borne out by the findings in the family of B. M. (Case II).

All of the patients reported in this paper had a hemoglobin value and a red blood cell count which were below normal. However, it is of distinct interest that Case I, A. W., was seen twenty-eight months before her last entry to the hospital, at which time her hemoglobin value and her red blood cell count were both within normal limits. The appearance of her red blood cells at that time

was just as characteristic as it was when she was last seen. Hence, we have positive proof that in this instance the shape of the cells cannot be attributed to the anemia, and it does not seem likely that the organic diseases from which she was suffering at this time could have been responsible for this unusual blood picture. Unfortunately, no relatives of this subject could be located. The active pulmonary tuberculosis would seem to offer sufficient explanation for the secondary anemia which was present at the time of the last examination. Case II, B. M., had a well-marked secondary anemia. The presence of elliptical cells in the blood of one of his children is strongly suggestive evidence that the peculiar shape of his cells was not due to the anemia, which was thought to be secondary to a neoplastic growth. The morphologic changes in the red blood corpuscles of Case III, L. A. B., cannot be proved to be independent of the mild anemia which was present, since there were no observations made of her blood when she had a normal level for her hemoglobin. And, further, the blood of none of her relatives was examined. However, I do not believe this type of poikilocytosis was due to the very slight anemia which this patient had. Abnormal variations in the shape of red blood cells are familiar findings in various types of anemia, but it is most unusual to find these changes in form to be all of the same type. In fact, it seems to me that changes in form of such uniformity as to produce a poikilocytosis characterized by extreme conformity of the abnormal shapes to oval or elliptical forms, should arouse the suspicion that there was an underlying developmental defect. In agreement with this, is the demonstration by Lawrence[9] and by Hunter and Adams[8] of the presence of these cells in normal relatives of 2 patients who have shown such abnormally shaped cells in their peripheral blood and at the same time have had low hemoglobin values. Further, Hunter and Adams[8] demonstrated that this poikilocytosis persisted in their patient even after the hemoglobin value had increased to 80 per cent, and the red blood cell count to 4,560,000 per c.mm.

It is interesting to speculate as to what effect this type of poikilocytosis may have on the production of anemia. The evidence at present does not permit any statement as to whether individuals with such a disorder develop anemia more readily than individuals with normal red blood cells. *A priori*, one would think that anemia might be produced in these subjects more easily than in normal subjects. Observations of a number of individuals with this anomaly over a long period of time will be necessary to settle this question. In this connection it should be stated that the 3 normal white subjects who were reported by Lawrence[9] as having sickle- and sausage-shaped cells had hemoglobin values which ranged between 75 per cent and 80 per cent. In other words, they were at the lower limits of normal. It would be of interest to follow these individuals over a long period of time to see whether they develop any appreciable

anemia. This morphologic peculiarity does not seem to be associated with increased rate of fragmentation of the red blood cells in the peripheral blood as evidenced by the normal fragility and icterus-index values which are found in this condition. But these findings do not exclude the possibility of other mechanisms being present which will tend to cause the appearance of anemia. In particular, the question of the effect of diet on such individuals is worthy of attention. It is entirely possible that individuals with this familial type of poikilocytosis may develop anemia much more readily, when on deficient diets, than will normal subjects. No experimental evidence on this question has been collected.

Since Sydenstricker, Mulherin and Houseal[11] had reported the finding of sickle-shaped and filiform erythrocytes in the bone marrow of patients with sickle-cell anemia, an examination of a specimen of bone marrow obtained from the sternum of Case II, B. M., was made. This revealed some sausage- and sickle-shaped cells but the evidence was not conclusive that these cells were actually in the bone marrow and not in the circulating blood of the bone marrow.

It is not possible to state whether this condition is related to true sickle-cell anemia. Certain it is, that many of the morphologic characteristics of true sickle-cell anemia are to be found in such individuals. On the other hand, there are certain distinct points of difference. For example, there is a definite tendency of the abnormal cells in this condition to show blunt rounded ends, whereas, in sickle-cell anemia, pointed ends are very frequent. Further, one may mention the absence of latent sickling and the failure of sickling to occur in the gas chamber of Hahn and Gillespie[6] in cases of elliptical and oval cells as contrasted with true sickle-cell anemia. Finally, the clinical syndrome occurring in sickle-cell anemia has not been found in the condition under discussion. Unquestionable sickle-cell anemia has never been found in a white subject, whereas the condition of elliptical and sickle-shaped cells in the peripheral blood has been found in both races. It seems reasonable, however, to assume that there may be some relationship between two conditions which have so many points in common.

Conclusions. 1. The occurrence in the circulating blood of sickle-shaped, elliptical and oval red blood cells has been reported in 3 patients. The blood of one child of one of these patients showed similar morphologic peculiarities.

2. A possible predisposition to anemia of individuals with such red blood cells has been discussed and it has been suggested that observations on individuals of this type over a long period of time might yield interesting data.

3. No positive evidence of a direct relationship of this condition to sickle-cell anemia has been presented, although the possibility of such a relationship must be considered.

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THE PROGNOSTIC SIGNIFICANCE OF THE LEUKOCYTE COUNT IN PNEUMONIA OF CHILDREN.

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The observation was so frequently made at The Children's Memorial Hospital that the pneumonias of infants and children with persistently low leukocyte counts usually terminated fatally that it was suggested by Dr. Joseph Brennemann that the daily leukocyte counts be followed in a series of pneumonias of infants and children to determine whether there existed a relationship between both the leukocyte count and its daily variation on the one hand, and the outcome of the disease on the other, that might be usable prognostic significance. No observations of the daily leukocyte count in pneumonias of infants and children were found in the literature although several studies have been reported by a number of observers in the lobar pneumonias of adults.[1] None of

these, however, included daily counts as in our series, none was limited to infants and children, and as far as we are able to determine, only lobar pneumonia was under consideration.

A series of 100 patients that were admitted to the hospital with pneumonia, taken consecutively from November, 1928, to May, 1929, are here presented from this standpoint. The patients were unselected except that only those were included in whom the diagnosis of pneumonia was made in each case by at least 2 attending physicians, and the findings in each case confirmed by Roentgen ray films of the chest. Those patients having other infections concurrent with pneumonia on admittance, such as suppurative otitis media, furunculosis, adenitis, pharyngeal abscess, at the onset of the observation period, were also excluded. Due to the well-known difficulty in accurately distinguishing clinically between lobar and bronchopneumonia in infants and young children, no attempt was made to classify the cases on this basis. While this may seem regrettable on the one hand, it offers on the other the compensating advantage of helping to determine whether there is a fairly uniform relationship between the leukocyte count and the outcome of pneumonia in children, regardless of the anatomic or bacteriologic type of the disease. If such a relationship would seem to appear from such an investigation, the deduction might perhaps more logically be made that a certain degree of illness itself has a corresponding leukocytic reaction rather than only certain types of infection, whether based on anatomic, bacteriologic or age factors.

Daily total and differential leukocyte counts were done on all of the patients in the series by the same individual, using the same pipette and counting chamber. A uniform method of counting the cells was followed throughout. The ear lobe was pricked by the same sharp instrument, the first drop of blood discarded, and only that taken which flowed freely without squeezing. In order to obtain uniformity and to approach accuracy, cognizance was taken of the daily physiologic variation of the leukocyte count. In order to obviate this possible source of error, each count was done the same time of each day. Sabin, at Baltimore, has demonstrated a normal physiologic variation of the leukocyte count of animals and human beings (adult).[2] Fletcher and Mitchell of Cincinnati studied the variation of the leukocytes in infants and children during twenty-four hours, finding that there was a definite cyclic fluctuation in the total leukocyte count at 2 to 4 P.M. and at 12 M. to 4 A.M. when the total number of leukocytes normally increased several thousand. This work is in accordance with Sabin and her workers in adults. Fletcher and Mitchell further concluded that any variation in the total leukocyte count which can be interpreted as a digestive leukocytosis is inconstant.

Of the 100 patients with pneumonia of our series, 30 died and 70 recovered. Fifteen of those that died had a white cell count of

less than 10,000 per c.mm., while only 3 with a count of less than 10,000 recovered. Twenty of the fatal cases had a count not exceeding 15,000, and all of these that lived long enough to make observations upon, showed a steady decrease in the leukocytes until death occurred. (Chart I.) In the 8 patients with counts under 5000 per c.mm., the count remained constantly low without any degree of fluctuation and none of these lived longer than the fifth day of the disease, the average being three days. Of the 10 fatal cases which had more than 15,000 cells per c.mm. at any count, 3 had a count which ranged between 50,000 and 70,000 cells per c.mm., and all of these died on the sixth or seventh day of the disease. Although there were but 3 patients of this group, it is noteworthy that all patients of the entire series who obtained so high a count were fatal. Of the remaining 7 cases terminating fatally, there was

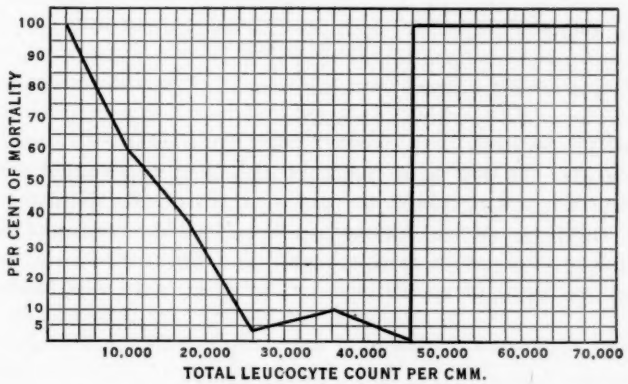

CHART I.—Relation of leucocyte count to mortality.

a relative degree of leukopenia or poor leukocyte response early in the disease with a sluggish tendency to rise (the highest to 20,000 cells per c.mm.) and all were characterized by a sudden drop in the total count. Two of this group developed empyema, whereupon the count rose rapidly to 40,000 to 50,000 before death.

Fifty-two patients recovered without complications and these were characterized by a good degree of leukocytosis throughout the illness, from 15,000 to 40,000 cells per c.mm. In these there was a uniformly gradual rise the first two to four days of the illness, remaining at a level for several days, and then decreasing slowly 2000 to 4000 cells per c.mm., per day one to three days before lysis or crisis of the fever (Chart II). This train of events was so consistent in these 52 patients that we were able to foretell the immediate progress of the illness two days before any clinical or physical change could be noted.

Of the remaining 18 patients that recovered, complications appeared five to ten days after the onset of the pneumonia. Eleven developed either unilateral or bilateral otitis media, 3 empyema, 3 extension of the pneumonic process into other lobes, and 1 developed a retropharyngeal abscess. In these patients the counts were

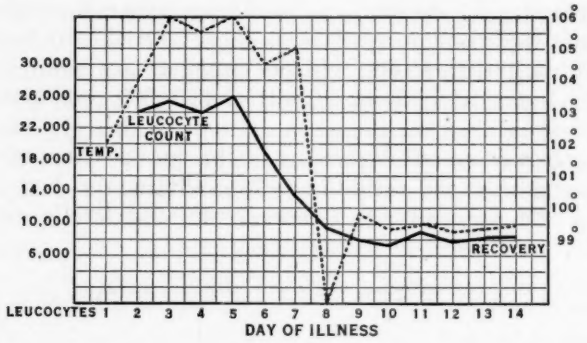

CHART II.—Relation of leucocyte count to day of illness without complication.

"normally" high at first, from 15,000 to 40,000 cells per c.mm., and followed the course of the uncomplicated cases until a sudden rise occurred, taking place at varying days of the disease. These sudden increases of the leukocytes appeared concomitant with or even before the rise in temperature, and one to two days before the physical signs of an otitis media or of an empyema were to be

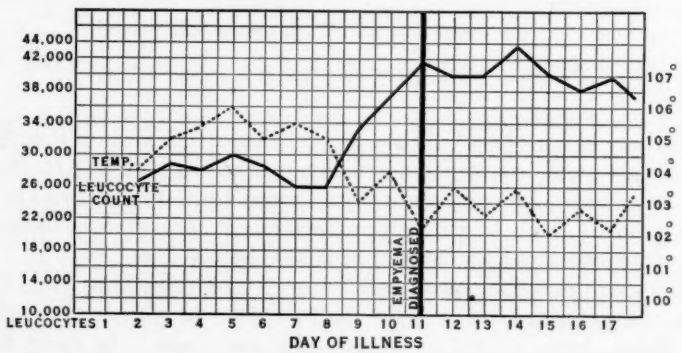

CHART III.—Relation of leucocyte count to day of illness in case with empyema.

observed (Chart III). The 2 patients demonstrating extension from one lobe to an adjacent lobe were most interesting, since both of the pneumonias were well limited to circumscribed portions of the lung as demonstrated by the Roentgen ray and physical findings. When the count rose from 22,000 and 24,000 to 34,000 and 31,000 cells

per c.mm. respectively on the sixth day of the diseases. The rise was accompanied by uniform physical and Roentgen ray findings of an involvement of the immediately contiguous lobes, the latter findings being found two to three days after the rise of the leukocyte count. An uneventful but prolonged leukocytosis occurred subsequently as convalescence progressed.

Of the 30 patients that died, 24 necropsies were obtained, which confirmed the clinical findings. There were 13 lobar pneumonias, 9 bronchopneumonias, and 2 empyemas originally diagnosed as lobar pneumonia. It is interesting to note that in one patient, a boy aged ten years, with a persistent leukopenia of less than 5000 cells per c.mm. throughout his illness, there was at necropsy a diffuse hemorrhagic pneumonia of the entire right lung. (Necropsy by Dr. W. H. Hibbs.) This pneumonia was not unlike that found in the fatal pneumonias during the pandemic of influenza in 1918, the finding of which was so characteristic of that disease entity. The only constant laboratory finding of epidemic influenza is said to be a leukopenia but the diffuse hemorrhages throughout the lung of a resultant fatal pneumonia were constantly found by the pathologists who performed hundreds of necropsies at the training camps during the last pandemic of influenza. This autopsy finding is so characteristic that Hirsch and LeCount[3] recently reported a case in an adult, suggesting that it might have been a sporadic interepidemic form of epidemic influenza. This finding in our patient is especially mentioned here because it was the only one of our series with a leukopenia that might have, clinically or pathologically been called true influenza pneumonia.

In this series of 100 patients, the youngest three weeks and the oldest eleven years, no demonstrable difference was noted in the ability of leukocyte response to infection as to age grouping or as to the type of pneumonia (broncho or lobar). The well-known fact of the relatively higher mortality in the infant group was evident.

	Under two years.	Over two years.
Recovered	19	51
Leukocytes under 15,000 per c.mm.	2	2
Leukocytes over 50,000 per c.mm.	0	0
Died	26	4
Leukocytes under 15,000 per c.mm.	16	4
Leukocytes over 50,000 per c.mm.	1	2

A daily differential leukocyte count was done concurrently with the total count, the differentiation being limited to polynuclear and mononuclear leukocytes. In these patients in whom there was an active leukocyte response to the pneumonia, the polymorphonuclear ratio was uniformly above 60 per cent even in the infants, and followed closely the rise and fall of the total leukocyte count. In those patients with a poor leukocyte response the proportion of

cells was more nearly that of the normal for the respective age. The appearance and the staining quality of the white blood cells were worthy of note. Those patients who had a low leukocyte count and were thought to be critically ill, had, in addition to the small number of leukocytes, a preponderance of degenerated polynuclear cells, the nuclei appearing fragmented and staining poorly, and the cytoplasm suggesting cloudy swelling. In the first few days of the illness when the white blood cells were rapidly increasing, there appeared many polynuclear cells which might be termed immature cells, with a large abundance of chromatin material and with large nuclei staining brilliantly.

As was stated previously, the prognostic significance of the leukocyte count has also been reported by a number of observers in the lobar pneumonias of adults, but no particular mention is made in the literature as to the pneumonias of infants and children. Nor has the significance of the leukocyte count in bronchopneumonia been observed as to the outcome. Chatard[4] in an analysis of 582 records of the Johns Hopkins Hospital in a period of sixteen years found a mortality of 50 to 60 per cent in those having a total leukocyte count under 10,000 cells per c.mm. With the rise in the total count, there was a progressive decrease in the mortality. From one to three blood counts were done on each patient during the course of the illness of this series. A similar result was obtained from an observation of the leukocyte counts in 463 cases of lobar pneumonia in adults at the Hospital of the Rockefeller Institute.[5] No statement was made as to whether daily counts were done throughout the illness on all of the patients, although several daily case reports are given. It was noted also by these workers that when consolidation by extension from one lobe to another occurred, there was a temporary increase of the leukocytes. They concluded that a steady rise in the leukocyte count is usually of favorable import, and if an initial low white count shows little tendency to rise, the prognosis may be grave. Bullow[6] and others, found that in 430 patients (adults) with lobar pneumonia, there was no relation between either the total or the polynuclear count and the outcome. They did observe however, that a degeneration of the leukocytes accompanied severe infections. No statement is made as to whether this series was followed by daily counts. Naegeli[7] mentions that very low and very high leukocyte counts are of ill portent in pneumonia, while von Wyss[8] questions any significance of the relation of the outcome of pneumonia to the blood count.

An observation worthy of mention was made during this study relative to the leukocyte counting and possible factors of error that are commonly supposed to exist in making a leukocyte count. In this series, between 1100 and 1200 separate total counts were made. After the count was made for the record, the opportunity was utilized to check the blood count. Counts were duplicated

from the same pipette of diluted blood and also duplicate counts were made from the original bleeding wound. With only moderate carefulness, if made at the same time, the count did not vary a 1000 cells, and more often less than 600 cells. Counts were also made simultaneously with the routine count of the intern on the service, and there was never a greater variation than 1000 cells, with the high counts not less than 700 in the low ones.

Fixed conclusions are not warranted from so small a series of patients but the results of this series are so surprisingly uniform that one is left strongly with the impression that the daily variation of the leukocyte count is at least a significant and valuable prognostic index in the pneumonias of infants and children, regardless of the type.

Summary. 1. In a series of 100 cases of pneumonia in infants and children, it was found that the mortality was inversely proportional to the leukocyte count, except that in children having over 50,000 cells per c.mm.

2. In this series of pneumonias, regardless of type, there is a relation between the lack of response on the part of the body in the production of leukocytes and a high mortality.

3. Evidence is presented which indicates that the total leukocyte count offers a valuable method of approximating the reaction of the host to the infection, and hence may be utilized as a prognostic aid.

4. Suppurative complications and extension of the pneumonia may be anticipated even in the presence of the primary pneumonia by the sudden increase of the leukocyte count.

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LEUKEMOID BLOOD PICTURE IN PSEUDOMUCINOUS CYST AND PAPILLARY ADENOMA OF THE OVARY.

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There are numerous infections which usually or at times produce a lymphocytosis. This increase may be so great as to suggest lymphatic leukemia. Upon other occasions there may be a depression

of the granular elements in the blood with no increase in lymphocytes or even with an actual decrease in their number. At other times there may not only be a depression of the granular elements but also lymphatic stimulation plus the evidence of bone marrow irritation. The picture of lymphocytosis in certain infections has become so well known that no further discussion is needed here. Since the work of Schultz in 1922 much interest has been aroused in the agranulocytic blood picture and it has now been reported to occur in other conditions aside from agranulocytic angina such as infections,[1] after antisyphilitic treatment,[2] inoculations for typhoid,[3] thrombopenic purpura,[4] and many other conditions with or without angina. In 1926 Krumbhaar[5] reported a series of cases in which there was evidence of lymphatic stimulation, depression of the granular elements and frequently abnormal cells such as monocytes, presumably indicating bone marrow irritation or intoxication. This blood picture he aptly termed leukemoid. His cases were grouped into the following classes: (1) Measles and pertussis. (2) Acute infections with lymphocytosis. (3) Acute infection with hemorrhage. (4) Terminal septicemia. (5) Bone marrow intoxication (mustard gas poisoning). (6) Agranulocytosis. (7) Myeloma. (8) Two indefinite cases with terminal leukemic blood pictures. These cases might at times have been confused with lymphatic leukemia but the clinical course or the autopsy decided the diagnosis differently.

The following case is reported as being of interest on account of the fact that the patient entered the hospital with a normal blood picture and that a leukemoid picture developed during her stay and was apparently terminated by the removal of a pseudomucinous cyst of the right ovary and a papillary adenoma of the left ovary.

Case Report.—Mrs. F., aged twenty-nine years, was admitted to Parkland Hospital, February 17, 1930, complaining of fever, pain in the head, back and extremities. Her past history was irrelevant except that she had had measles and pertussis. Her present illness began two days before admission with cold in the head, cough and fever. The temperature on admission was 103, pulse, 122; respiration, 22. Her general examination showed the nose, pharynx and tonsils to be moderately inflamed. The appearance of the throat did not suggest influenza. There were a few scattered dry râles in the chest. The spleen and lymph glands were not enlarged. There was a large mass in the abdomen extending from the pelvis to the umbilicus which the patient had not noticed. The laryngologist reported "Hypertrophied middle turbinates. Submerged tonsils. Marked pyorrhea. Sinuses clear." The gynecologist's report was that the abdominal mass was probably a cyst of the right ovary although pregnancy must be suspected. Roentgen ray examination showed no fetus. The sinuses were also clear by Roentgen ray examination.

Laboratory findings on admission showed: Blood; hemoglobin, 80 per cent; red blood cells, 3,900,000; white blood cells, 7,100. The differential count was neutrophils, 65 per cent; lymphocytes, 32 per cent; eosinophils,

1 per cent; basophils, 2 per cent. The urine was negative. No malaria parasites were found by the concentration method. The Widal was negative for typhoid and paratyphoid, as was the agglutination for Bacillus melitensis and abortus. The Wassermann was negative.

During the first week in the hospital her temperature varied from 99° to 102° F. and she presented the picture of a respiratory infection with rather marked febrile response. Her temperature fell to normal at the end of the week. A few days later, while preparation was being made for her operation, she became tender over the lower abdomen. There was no fever, no vomiting, or rigidity but a blood examination made at that time showed 18,450 leukocytes; neutrophils, 15 per cent; lymphocytes, 85 per cent; no abnormal cells. A count made the next day showed 13,400 leukocytes; neutrophils, 16 per cent; lymphocytes, 79 per cent; metamyelocytes, 1 per cent; lymphoblast, 1 per cent; mononuclears, 3 per cent. In view of this blood picture operation was deferred. The complete blood count will be given below. March 19, twenty-three days after admission she had a sore throat with slight fever. There was a filmy exudate on the right tonsil. A smear from this showed spirochetes and fusiform bacilli. This yielded promptly to treatment. On the 26th, a laparotomy was performed by Dr. Sam D. Weaver who removed a large pseudomucinous cyst of the right ovary and a papillary adenoma of the left ovary. Nothing further was

Date.	Hemoglobin percentage.	Red blood cells.	White blood cells.	Neutrophils.	Lymphocytes.	Eosinophils.	Basophils.	Metamyelocyte.	Lymphoblast.	Mononuclears.
Feb. 17, 1930	80	3,960,000	7,100	65	32	1	2			
Feb. 21, 1930	80	4,120,000	5,750	43	50	1	1			
Feb. 22, 1930	..	....	6,350	48	52					
Feb. 24, 1930	..	....	8,800	48	52					
Mar. 2, 1930	85	....	**18,450**	**15**	**85**					
Mar. 3, 1930	80	4,020,000	13,400	16	79	..	..	1	1	3
Mar. 5, 1930	80	3,990,000	13,400	27	73					
Mar. 6, 1930	..	....	11,500	31	60	2				
Mar. 7, 1930	..	....	9,950	24	74	..	..	..	..	2
Mar. 8, 1930	..	....	10,850	29	70	..	..	..	..	1
Mar. 10, 1930	..	....	7,600	34	65	1				
Mar. 11, 1930	..	....	9,100	39	60	1				
Mar. 12, 1930	..	....	9,900	31	65	4				
Mar. 13, 1930	..	....	8,700	27	67	5				
Mar. 14, 1930	..	....	8,050	44	56					
Mar. 15, 1930	..	....	....	52	47	1				
Mar. 17, 1930	..	....	....	49	51					
Mar. 18, 1930	..	....	....	30	63	4	1			
Mar. 19, 1930	..	....	....	50	46	3				
Mar. 21, 1930	80	3,930,000	7,450	36	59	4				
Mar. 22, 1930	75	3,860,000	9,100	32	67	..	1			
Mar. 24, 1930	80	3,900,000	8,200	54	61	1				
Mar. 31, 1930	75	3,650,000	6,900	54	40	5				
April 3, 1930	80	3,900,000	9,350	47	45	4	4			
April 9, 1930	80	3,870,000	7,000	36	61	3				
April 14, 1930	80	3,970,000	6,600	60	39	1				
April 26, 1930	75	3,690,000	6,800	56	40	1	1			
May 21, 1930	80	4,550,000	6,300	62	29	2	2			

found in the abdominal cavity. The operative diagnosis was confirmed by Dr. George Caldwell. The patient made an uneventful recovery. The blood picture remained unchanged for some time with an average of 7,000 white cells, of which 40 per cent were lymphocytes. This picture slowly improved until May 21, about two months after the operation, her blood picture was as follows: Hemoglobin, 80 per cent; red blood cells, 4,550,000; white blood cells, 6,300; neutrophils, 62 per cent; lymphocytes, 29 per cent; eosinophils, 2 per cent; basophils, 2 per cent. The complete blood counts are given below. The percentages do not check entirely since unidentified cells and degenerated cells are not listed.

Comment and Summary. It is felt that the original infection which brought the patient to the hospital was not a factor in producing the blood picture. She had recovered entirely when this developed. The finding of Vincent's organisms, together with the sore throat and especially since she had pyorrhea, might be thought to have some effect except for the fact that her blood picture showed no change at the time this appeared. At the time that the change in the blood picture occurred she developed abdominal tenderness. It is possible that she had peritoneal irritation which could perhaps produce this blood picture. It may further be that the nature of the growths themselves could account for the blood changes although no reports concerning this could be found. The blood picture itself scarcely shows enough in the way of abnormal cells to suggest leukemia but the percentage of lymphocytes was greater than is usually found in a simple lymphocytosis. At a later stage when there was a relative and absolute decrease in the granular elements a suspicion would naturally arise that agranulocytosis might develop. It is well known that following a leukocytosis the lymphatic elements decrease more slowly than the granular ones. In this case however, this decrease remained stationary until after operation, but began shortly thereafter and continued slowly until a normal picture was reached.

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PANCREATITIS COMPLICATING MUMPS.

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Pancreatitis as a complication of mumps has been reported mainly in the French literature. Cuche[1] in 1897 described 20 cases of mumps in which there were symptoms of pancreatic involvement. Six years later Simonin[2] reported 654 cases of mumps admitted over a period of four years to the military hospital of Val de Grace. Ten of these were complicated by pancreatitis. Moutier[3] in a comprehensive study of 600 cases of mumps found 74 instances of pancreatitis, 49 of which were very mild. Dopter[4] observed pancreatic involvement in 45 of his series of 800 cases. Freund[5] collected 8 cases of pancreatitis during an epidemic of mumps in a rural section near Vienna. In this country Radin[6] mentioned the occurrence of symptoms referable to pancreatic involvement in 14 of his large series of almost 6000 cases at Camp Wheeler in 1918. In most critical reviews of the subject pancreatitis is considered as unusual or rare.[7]

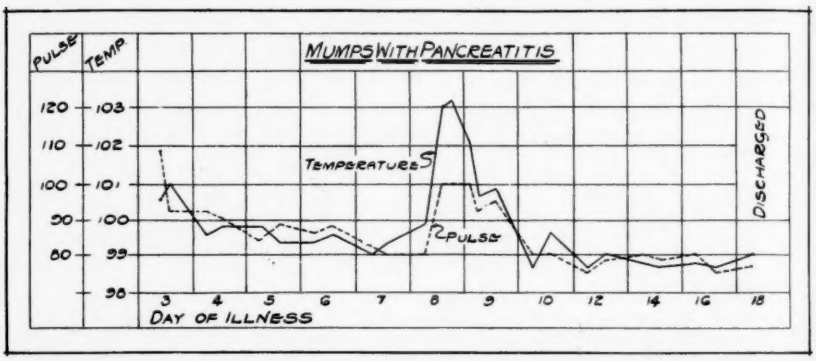
Number of Cases of Mumps Reported in New York City, 1920 to 1929, and Number Hospitalized in Contagious Disease Hospitals in New York City, 1925 to 1929.

	No. cases in entire city.	Cases hospitalized.	
		Number.	Per cent.
1920	959		
1921	3627		
1922	3108		
1923	3817		
1924	5892		
1925	1273	39	3.0
1926	3263	82	2.5
1927	9668	333	3.4
1928	1420	76	5.4
1929	6523	306	4.8

In New York during 1929 there was an epidemic of mumps. The total number of cases in that year was exceeded only once (1927) in the last ten years (see table). Mumps is considered such a mild disease that very few cases are sent to the hospital. The percentage of reported cases hospitalized in the contagious disease hospitals in New York varies from year to year and is between 2.5 and 5.5 per cent (see table). During 1929, 80 per cent of the hospitalized cases were in the Willard Parker Hospital. Among the 252 patients admitted to the Willard Parker Hospital with mumps

between January 1, 1929, and March 1, 1930, 42 developed complications as follows: orchitis, 27; pancreatitis, 13; meningitis, 2 and thyroiditis, 1. Because of the unusual frequency of pancreatic involvement in our cases and the characteristic symptom complex associated with it, we shall describe the condition in detail.

Thirteen of the 252 patients developed pancreatitis from three to nine days after admission to the hospital. Five were males and 8 females. Only 3 of our patients were under ten years of age; the youngest was six years, the oldest thirty years and the average age incidence was seventeen years. The complication occurred from the fifth to the eleventh day of the illness, with an average time of onset during the seventh day. Both parotid glands were involved in all except 1 case. In only 1 instance—that of a man who also had orchitis—was there any other complications in those patients with pancreatitis. All patients made a complete recovery.



Typical temperature and pulse chart in case of mumps complicated by pancreatitis.

The patients became acutely ill with nausea, anorexia and fever. The temperature rose for one or two days and usually reached between 103° and 104° F. In only 2 patients did the temperature remain below 103° F. After reaching the fastigium the temperature decreased and was normal on the third to the fifth day. The pulse was usually slow in relation to the temperature (see chart). The patients complained of malaise, nausea and abdominal pain. The pain was epigastric in most instances, but sometimes it was in either the right or left hypochondrium and occasionally over the entire upper abdomen. Vomiting occurred frequently but was not severe. Five of the 13 patients complained of moderate headache. Most of the patients were constipated; diarrhea and steatorrhea did not occur. All of our patients had tenderness over the upper abdomen. The abdominal wall was relaxed but no abnormal masses were palpable. The urine was sugar-free in all cases. Neurologic examinations and gross tests for hearing failed to reveal involvement of the nervous system or the ears. Rectal or vaginal examinations were done to exclude involvement of the ovaries.

The symptomatology of mumps pancreatitis was carefully studied by Simonin[2] at a military hospital in France. His cases were milder than ours but corresponded in most points to the symptomatology found in our series. Epigastric pain was usually the first symptom observed by Simonin, whereas we found nausea, anorexia and malaise the initial symptoms. A few minor points described by Simonin, such as pain referred to the lumbar and interscapular regions, diarrhea and presence of bile in the stools were absent in our cases. Four of his cases were afebrile, representing a mild form of pancreatitis which we did not encounter. Jacob[8] and Edgecombe[9] each reported a case in which the enlarged pancreas was palpable. Although there was no spasticity of the abdominal wall in our patients we were unable to palpate any abnormal masses.

Classification. The variation in the extent of the involvement of the pancreas led Moutier to classify the condition into mild, moderate and severe forms. In the mild form there is transient pain and tenderness in the region of the head of the pancreas. The moderate form includes those cases with fever, vomiting, digestive disturbances (constipation or diarrhea) and abdominal pain and tenderness. The severe form shows evidences of more extensive pancreatic involvement such as glycosuria or hyperglycemia. All of our cases were of the moderate form. An unusual chronic type was reported by Merklen and Gourelle.[10] Their patient was a twenty-eight-year-old female whose parotid swelling was followed in a few days by the symptom complex of pancreatitis. The pain in the epigastrium and left hypochondrium persisted for twenty-three days, and diarrhea was present for nineteen days. During the following five months she had three attacks of pain just below the left costal margin, associated with anorexia and diarrhea.

Differential Diagnosis. Pancreatitis may be confused with other complications of mumps. In mumps meningitis the fever is usually not as high, nor is vomiting as frequently present as in pancreatitis. Nausea and upper abdominal pain and tenderness are absent. The stiffness of the neck and the abnormal and exaggerated reflexes found in meningitis do not occur in pancreatitis. The aural complications of mumps begin in some cases with nausea, vomiting and slight fever[11] but none of the symptoms are as severe as in pancreatitis. Headache occurs with about the same frequency in each condition. The presence of vertigo, tinnitus and impaired hearing and the absence of abdominal pain and tenderness should make the differentiation evident. In female patients, oöphoritis must be excluded. The patients with oöphoritis have a lower temperature, as a rule do not vomit and have pain and tenderness, often unilateral, in the lower abdomen. Rectal or vaginal examination usually reveals an enlarged and tender ovary, a condition not found in pancreatitis.

Pathology. There are only 2 autopsy reports of cases of mumps with pancreatic involvement. The first was reported by Lemoine

and Lapasset[12] in 1905. Their patient was a soldier, nineteen years of age, with bilatoral mumps, who developed a typical syndrome of pancreatitis on the fifteenth day of his illness. He rapidly became icteric, vomited persistently and died following a profuse hematemesis. Postmortem examination revealed that enlarged lymph nodes had compressed the common bile duct and portal vein. The findings in the pancreas were recorded as follows: "The pancreas shows an abnormal increase in volume, weighs 190 gm., is edematous, congested and reddish-gray in color, apparent even on section of the gland. The lymph nodes about the gland are abnormally swollen, but those in the lumbar region and in the mesentery are normal in in size. The pancreatic ducts and ampulla of Vater are normal in appearance and readily permit the passage of a probe. Histologic examination with low-power magnification gives the impression of a normal gland. There are no nodules of embryonic cells or extravasations of blood. Under high-power magnification the cells have a clear outline such as is rarely seen in a normal pancreas, probably due to the immediate removal of the gland after death. Many of the parenchymatous cells are vacuolated. The nuclei contain little chromatin and stain poorly. The acini are swollen and their lumen considerably enlarged. The islands of Langerhans are reduced in size and number, due to compression by the glandular elements."

The only other postmortem report is by Sabrazes, Broustet and Beaudiment.[13] Their patient was a nineteen-year-old male, who escaped from a military hospital on the fifth day of his illness. The following day he returned to the hospital exhausted and in distress. His temperature was normal, his pulse rapid and feeble, he vomited and complained of epigastric pain. He died two days later with signs of acute nephritis and pulmonary congestion. Postmortem examination showed involvement of the entire pancreas. The gland was increased in volume. The surrounding lymph nodes were hyperplastic. There was evidence of fat necrosis in and about the pancreas. There was massive coagulation necrosis of the parenchymatous tissue and an interstitial edema. Some of the few islands of Langerhans which were found showed degenerative changes. There was neither thrombosis, nor hemorrhagic effusion. Bacteriologic examinations were negative.

Wollstein[14] reported the pathologic changes in the parotid glands of monkeys in which she had produced mumps experimentally. In many points the changes observed by her correspond to those found in the pancreas in the 2 cases cited above. The experimentally infected parotid glands were pink in color, enlarged and edematous. The epithelium of the acini was swollen and cloudy and some of the ducts were dilated. These changes correspond closely to those observed by Lemoine and Lapasset in the human pancreas. The few differences are probably due to a more intensive infection in the fatal human cases. In these there was more edema and the parenchymatous cells showed more advanced changes such as loss of

chromatin and staining power and the presence of vacuoles. The lymph nodes around the pancreas were greatly enlarged in contrast to the slight enlargement reported by Wollstein in her study of the parotid glands. This may have been due either to differences in the virulence of the infection or to differences in the lymphatic drainage of the two glands. The pancreas in the case of Sabrazes, Broustet and Beaudiment, was also increased in volume due to an interstitial edema. The parenchymatous changes, however, consisted of an actual massive coagulation necrosis, a much more advanced lesion than the one found by Lemoine and Lapasset.

Case Reports.—Case I. B. B., a female, Porto Rican, aged eighteen years, was admitted to the Willard Parker Hospital on November 11, 1929, with marked swelling of both parotid glands of three days' duration. Her temperature was 99.4° F., pulse 98, and respiration 20. Two days later the temperature was normal. On the sixth day of her illness (third day in hospital) the patient complained of headache and vomited once. The following afternoon the temperature rose to 103.2° F., and pulse to 120, the respirations were normal. The swelling of the parotid glands had decreased considerably. The patient complained of general malaise, headache, epigastric pain, was nauseated and vomited twice. During the following two days (eighth and ninth days of illness) the malaise, headache, nausea and vomiting persisted, but with decreasing intensity. The patient was constipated. The temperature ranged between 99° and 100.8° F. Physical examination showed a moderately ill patient with tenderness in the epigastrium, more marked to the right of the midline. There was no jaundice. Vaginal examination for oöphoritis was negative. After the tenth day of the illness the temperature remained normal, the patient was comfortable and made an uneventful recovery.

Case II.—T. B., a white female, aged twenty-three years, was admitted to the Willard Parker Hospital on June 23, 1929, with swelling of both parotid and the right submaxillary glands of three days' duration. The temperature was 100° F.; pulse 80 and respiration 20. The temperature, pulse and respiration were normal after the third day in the hospital and the glandular swelling decreased rapidly. On the seventh day of her illness the patient complained of malaise, nausea, headache, and upper abdominal pain. The temperature rose to 103.6° F., and the pulse to 108. Physical examination revealed a soft abdomen with tenderness in the epigastrium and right hypochondrium. The liver edge was palpable; the spleen was not felt. There were no abnormal masses. There was no jaundice. The following day (ninth day of illness) the pain and nausea persisted, the temperature rose to 103.2° in the morning but fell below 100° F. in the afternoon. On the tenth day the patient vomited but her general condition was better. The temperature was 101° F. Two days later the temperature was normal, the patient felt well and made an uneventful recovery.

Case III.—I. B., a white male, aged thirty years, was admitted to the Willard Parker Hospital on June 26, 1929, with swelling of both parotid glands of two days' duration. The temperature was 101° F. pulse 90 and, respiration 22. The swelling subsided after a few days but the temperature remained between 100.2° and 100.6° F. On the seventh day of his illness, the patient complained of nausea, headache and abdominal pain. The temperature rose to 103.6° and remained at that level until the next morning, but fell to 101° F. in the afternoon. The abdomen was soft and slightly tender. Headache, nausea and abdominal pain persisted for two more days.

The temperature on the ninth and tenth days was 100°, after which it remained normal. The patient had no further complaints and made an uneventful recovery.

Summary. Pancreatitis complicating mumps produces a characteristic symptom complex. It occurs in both sexes and at any age. In our series the extremes of age were six years and thirty years. The onset is sudden between the fifth and the eleventh days of the illness with nausea, anorexia and fever. The temperature rises in a day or two to 103° or 104° F. in the moderately severe cases, and returns to normal in three to five days. The pulse is usually slow in relation to the temperature. The patients complain of malaise, nausea, headache and abdominal pain and usually vomit. The pain and tenderness in our cases were always in the upper abdomen. Most of our patients were constipated, and diarrhea which has been reported by other observers did not occur in our series. There was no glycosuria. Information from autopsy examinations is limited to 2 cases. The pathologic changes in the pancreas reported by Lemoine and Lapasset are comparable to the changes found by Wollstein in the parotid glands of monkeys experimentally inoculated with mumps. The abnormal findings in the pancreas described by the French authors are in all probability only a little more advanced than those which occur in the patients who recover.

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SPLENOMEGALY AND HEPATIC ENLARGEMENT IN HEREDITARY HEMORRHAGIC TELANGIECTASIA.

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Since the case report and review of the literature of hereditary hemorrhagic telangiectasia recorded by the author[1] in 1923, 4 additional unrelated patients with the disease have come under observation. Study of these patients has revealed certain features not heretofore emphasized in the annals of this obscure disorder. These features are: (1) Splenomegaly and hepatic enlargement; (2) increasing intolerance to blood transfusion, and (3) the interesting coincidence of identical blood group ("0" or Type IV, Moss) in all of those tested (that is, 3 of the 4 cases to be reported together with an additional afflicted relative of one of these patients and also the only similar "typed" case reported in the literature and discussed below).

Case Reports.—Case I. Mr. Max G. was first admitted to the University Hospital, service of Dr. Edsall, on December 6, 1910. At this time the patient was forty-four years of age. He went through a somewhat atypical left upper lobe pneumonia and was discharged "cured" on January 5, 1911, with, however, a questioned diagnosis of underlying pulmonary tuberculosis appended. At this time his blood count was normal except for initial leukocytosis. Spleen and liver were "not palpable." There was no notation of personal or familial hemorrhagic disorder except a statement of "troublesome expistaxis." No telangiectases were noted.

Second admission, aged fifty years, August 25, 1917, to September 21, 1917, service of Dr. Stengel. Again the patient went through an attack of lobar pneumonia. At this time he was found to have *definite enlargement of the spleen* (Dr. Pepper) and while on the ward several "profuse hemorrhages from the nose and mouth" occurred which were interpreted as presumptive evidence of tuberculosis although no tubercle bacilli were found. He was discharged with a marked anemia (red cells, 3,240,000; hemoglobin, 45 per cent.) Still no notation in the records is to be found of telangiectases or of familial hemorrhages.

Third admission, aged fifty-eight years, April 19, 1924, to May 21, 1924, service of Dr. Stengel. For the first time in this record we now find a frank history of personal and familial hemorrhages, the notation of typical telangiectases and a diagnosis (Dr. R. A. Kern) of hereditary hemorrhagic telangiectasia. The spleen was again noted as palpable and the liver also. The author's contact with the case dates from this admission.

Fourth admission, aged sixty-two years, September 18, 1927 to October 5, 1927, and final admission, aged sixty-three years, December 20, 1929 to January 18, 1930 (death and autopsy).

Sumary of Pertinent Data. Mr. M. G. (Jewish) began to have epistaxis at the age of about twenty-five to thirty years. Telangiectases of lips and face were first observed by the patient at about forty years of age. Recurrent epistaxis marked his life until the end. Anemia is first known to have

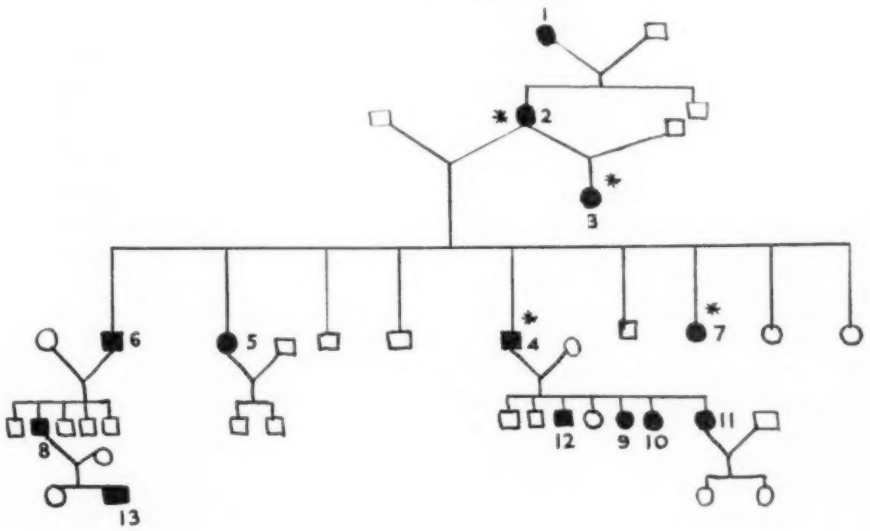
occurred at the age of fifty, when also definite splenomegaly was noted. Hepatic enlargement is first recorded at the age of fifty-eight. Epistaxis and occasional hemoptysis were the only hemorrhagic manifestations until about sixty years of age, when profuse melena occurred. No hematuria. No petechiæ. No abnormal posttraumatic bleeding. The patient received his first transfusion in another hospital in 1929 and apparently suffered no severe reaction. For his next blood transfusion the donor was his son, also mildly afflicted with epistaxis and of the same type (group "0"). This was given (citrated) on December 26, 1929 with moderate immediate reaction but with persisting low fever thereafter and with increasing obstructive jaundice until death. The third and last transfusion (from another relative of identical blood type) was given on January 17, 1930, following which the previously enlarged liver became suddenly smaller, and diarrhea, chills and vomiting marked the terminal picture. Death occurred the next day, January 18, 1930.

Numerous blood counts, from the time of the third admission, showed increasing hypochromatic anemia with normal leukocyte picture. Platelet counts, bleeding time and venous blood coagulation-time tests were repeatedly normal. Clot retraction normal, tourniquet test, negative. Erythrocyte fragility test, B. H. 0.425–C. H. 0.300. Phenoltetrachlorphthalein liver-function test April 20, 1924 gave normal results (5 per cent retention after fifteen minutes—zero retention after sixty minutes). Blood Wassermann tests were repeatedly negative. Rhinoscopic examination showed typical telangiectasis—which were also present as papules on lips and tongue and as "spider forms" on face. Cystoscopy (1924) was negative for telangiectases. Bronchoscopy (Dr. G. Tucker) in 1924 showed "distinct telangiectases which bleed on the slightest pressure in the trachea and left bronchus." Proctoscopy (Dr. I. S. Ravdin) 1924—"entire mucosa of rectum as far up as sacral promontory is speckled with lesions which look like tubercles." Biopsy specimen of rectal mucosa showed these lesions to consist of "numerous areas of telangiectasis." The telangiectases on lips and tongue were tested by local application of vasoconstrictor substances (adrenalin, cocain, ice, and so forth) without results—indicating probable lack of the normal neuromuscular control of these thin-walled vascular defects.

On final admission to hospital, the patient's blood count was: reds, 1,800,000; hemoglobin, 17 per cent; reticulocytes, 4.8 per cent. Moderate poikilocytosis and polychromasia and an occasional myelocyte seen. Coagulation factors all normal. Van den Bergh test (December 23, 1929, prior to development of terminal jaundice) was normal (direct, 0; indirect, ±0.2 units). Hematocrit reading gave 16 volumes per cent of cells. The color index was 0.48 and volume index 0.88. Blood fibrinogen was 340 mg. per 100 cc. of plasma and 285 mg. per 100 cc. of whole blood. Fragility test at this time again was normal. Liver function test December 25, 1929 (bromsulphthalein) showed 30 per cent retention after five minutes and 5 per cent retention after thirty minutes. The blood was Group 0 (Type IV, Moss). At this time the spleen was large and soft and extended 10 cm. below ribs, and liver was firm and smooth and extended also 10 cm. below ribs. Four days after transfusion, December 26, 1929 and for the first time in the patient's life, jaundice was noted. This became steadily worse and soon was complete (acholic feces and urine loaded with bile). On January 6, 1930, the van den Bergh reaction was direct, biphasic; indirect, 11.2 units. Icterus index was then 60. Fasting blood sugar, 0.114 per cent. Serum protein was 6.040 per cent. Just prior to death (following the last transfusion) the liver became markedly smaller and the urine showed a few tyrosin crystals—suggesting terminal acute yellow atrophy.

Summary of Autopsy Report (Dr. Custer): Mr. M. G., January 18, 1930. "The skin shows intense jaundice and there are no other external abnormalities." (Note: Telangiectases were present on lips and face, which were obvious and repeatedly described during life.) "All viscera show marked jaundice." Heart essentially negative except for "brown atrophy and fatty degeneration." Small scar of healed tuberculosis at right apex. Moderate pulmonary edema. "No tracheal or bronchial telangiectases." (Note: Bronchoscopy in 1924 had revealed numerous telangiectases—this means therefore that telangiectases had doubtless disappeared from this region as is known to occur occasionally in cutaneous lesions.) *The spleen*

CHART OF MAX G'S. FAMILY HISTORY SHOWING TYPICAL HEREDITARY. NO ATAVISTIC INSTANCES APPARENT.



●—females
■—males
} with epistaxis (and telangiectases?)

□—males
○—females
} unafflicted.

* Known to have died of the disease, Nos. 2, 3, 4, 7.

1. Patient's maternal grandmother. 2. Patient's mother (who married twice). 3. Patient's half sister. 4. Patient Mr. M. G., 5, 6, 7 siblings of the patient. 8. Nephew of patient. 9, 10, 11, 12. Children of the patient. 13. Grand-nephew of patient.

measured (when removed) 19 by 13 by 7 cm. and weighed 660 gm. Its color was slate gray and its consistency "rubbery." Cut surface was "dark red" and "streaked irregularly with hyaline-like material" which did "not give the color reaction for amyloid." Histologic study of the spleen showed nothing but "chronic hyperplasia; fibrosis" and numerous "areas of hemorrhage." The liver was "mottled" in appearance and was smaller and firmer than normal. It weighed 1300 gm. and measured 23 by 16 by 7 cm. There was no gross ductal obstruction. The gall bladder was thickened and contained "black inspissated bile." Histologic examinations of the liver showed nothing except "toxic hepatitis" and some evidence of "bile

capillary obstruction." No ascites. Kidneys showed "cholemic nephrosis." Esophagus was negative except for petechiæ in mucosa. Stomach and small intestine—normal. The cecum, colon, sigmoid, and rectum showed "homogeneous blue-black discoloration of the mucosa, beginning abruptly at the ileocecal junction." No ulcerations and no telangiectases. Microscopy showed nothing except "melanosis and edema." (Note: Again compare the proctoscopic and biopsy of the rectal mucosa in 1924. The melanosis found at autopsy perhaps represents an end stage of telangiectatic degeneration.) Urinary bladder normal. Pancreas and adrenals normal. *Bone marrow* (mid femur) showed "intense hyperplasia."

Summary Comment, Case I. A typical instance of hereditary hemorrhagic telangiectasia presenting in addition the following noteworthy features. (1) Splenomegaly which developed before fifty years of age and after twenty years of moderately severe recurrent epistaxis and prior to blood transfusion. (2) Hepatic enlargement, which was first noted at age of fifty-eight years (also prior to first transfusion) and which was symptomless until after second blood transfusion. Jaundice and cholemia then appeared and finally, after third transfusion, the picture of acute atrophic toxic hepatitis terminated the story. (3) Increasing intolerance to blood transfusion ending in death within twenty-four hours of the third transfusion. (4) The patient's blood was of Group 0 (Type IV, Moss). One of his afflicted sons and one nonafflicted son also belonged to the same group. (5) The actual demonstration during life of telangiectases in the bronchial tree and in the rectal mucosa, which could not be demonstrated postmortem four years later.

Case II.—Mrs. J. L. G. was first seen on April 23, 1927, at the University Hospital, through the courtesy of Dr. Stengel. Mrs. G. (then forty-six years of age) presented a typical history of hereditary hemorrhagic telangiectasia affecting her father, two brothers, and two of her children. She, herself, had suffered the usual recurrent epistaxis since childhood, and first noted telangiectases in her lips and face in early adult life. Not until 1925, at the age of forty-four, did she begin to suffer from severe constitutional symptoms. Then for the first time anemia was marked.

Physical examination April 23, 1927, revealed subicteric pallor, tachycardia, a functional systolic bruit at cardiac apex, slight edema of feet, a readily palpable spleen (2 inches below ribs) and liver (1½ inches below ribs) together with typical telangiectases of lips, face and intranasal mucosa. There were no pectechiæ or enlarged lymph nodes. Blood count, April 23, 1927: red cells, 2,500,000; white cells, 4000; hemoglobin (Sahli), 30 per cent. Polymorphonuclear neutrophils, 71 per cent; lymphocytes, 17 per cent; monocytes, 7 per cent; eosinophils, 5 per cent. *Platelet count* 130,000 per c.mm. in counting chamber, but obviously more abundant than this in the stained smear. Marked poikilocytosis, polychromatophilia and anisocytosis with moderate basic stippling and 2 normoblasts per 100 leukocytes. No macrocytosis. No megaloblasts. Color index 0.6. Other hematologic tests were normal (bleeding and clotting time, clot retraction, erythrocyte fragility, and so forth). The blood Wassermann test was negative. Urinalysis essentially negative. The patient's blood was of Type IV (Moss classification). The accessible intranasal telangiectases were cauterized by Dr. George Fetterolf and in addition the patient received three blood

transfusions (each 500 cc. of citrated blood) within a period of two weeks. These transfusions produced very little reaction.

After discharge from the hospital the patient soon became very weak again and moderate epistaxis recurred. In spite of the fact that she took adequate liver diet and large doses of iron regularly, her blood count fell steadily so that four more blood transfusions were deemed necessary by her family physician. Following each of these (citrated) transfusions (from Type IV donors) she suffered severe reactions characterized by fever and delirium and slight jaundice.

She returned to Dr. Stengel's care in the University Hospital on January 12, 1928, for a trial of massive Roentgen ray irradiation of the spleen.[2] At this time physical findings were similar except the spleen and liver were larger than before. During the next few months the patient received several courses of Roentgen ray therapy over the spleen without benefit. Again, as before, a potent liver extract and iron medication failed to keep her blood count up in spite of the fact that she had very slight further nasal hemorrhages and no other discoverable blood losses (that is, no melena, no hematuria, no menorrhagia). In April, 1929, her family physician Dr. F. D. Reckord reported her blood count as: red cells, 1,600,000; white cells, 7000, and hemoglobin, 22 per cent. He also reported that her liver was enlarged down to the umbilical level but that no ascites was present. She was given three more transfusions in May, 1929, with similar reactions. On December 3, 1929, another transfusion was necessitated by the marked weakness, dyspnea and anemia and the patient died ten hours later in coma and "shock." Autopsy was not obtainable.

Summary Comment, Case II. Again we have a typical case of hereditary hemorrhagic telangiectasia, presenting in addition the following noteworthy features: (1) Splenomegaly and hepatic enlargement discovered at age of forty-six—after about thirty years of recurrent epistaxis and prior to any blood transfusion. (2) Increasing intolerance to blood transfusion ending in death with jaundice ten hours after last transfusion. (3) Anemia out of proportion to demonstrable blood loss. (4) The patient's blood was of Group 0 (Type IV, Moss).

Case III.—Mrs. S. L., was admitted to the ward service of Dr. Stengel on September 14, 1924 and discharged September 26, 1924. She was then forty years of age. She had suffered from recurrent epistaxis since her twenty-first year and in addition had had occasional bleeding from "spots on her tongue." Four years previously she had severe melena which necessitated a blood transfusion. She first noted "spider" veins on her face and "red spots" on her lips and tongue in 1921. Her father suffered from epistaxis but lived to eighty years of age. Physical examination revealed pallor and dyspnea and sanguineous discharge from nose. Telangiectases were noted on tongue, palate, uvula, lips, cheeks, nose, forehead, neck, abdomen and under nail beds. All these lesions blanched under pressure. The spleen was "readily palpable" about 5 cm. below ribs. The liver edge was palpable. No ascites. Blood studies (September 15, 1924): reds, 4,000,000; whites, 7000; hemoglobin, 30 per cent. Coagulation time, four minutes (venous). Bleeding time, one minute. Tourniquet test, negative. Platelets, 180,000. Blood, Type IV, Moss. Blood Wassermann, negative. A transfusion of 400 cc. of citrated homologous blood was given on September 17, 1924 which was followed by *increased* epistaxis, chills and fever, and, the next day, by jaundice. The continued epistaxis required packing

of the nose and from this the patient developed otitis media, which gradually subsided as did the jaundice. The patient signed her release and left the hospital on September 26, 1924. Her subsequent course is not known.

Letters from two hospitals in the city in which the patient had been treated gave their diagnosis as "purpura hemorrhagica" which is the one most often incorrectly applied to these cases.

Summary Comment, Case III. Another typical example of hereditary hemorrhagic telangiectasia with splenomegaly and intolerance to blood transfusion belonging to Group 0 (Type IV, Moss).

CASE IV.—Mrs. S. was referred by Dr. K. M. Houser on July 18, 1929. She was then fifty-eight years of age. Her personal and family history were perfectly typical and physical examination revealed the usual telangiectatic spots in labial and nasal mucosa and in skin of face, hands and neck. Epistaxis had been recurrent since adolescence. Her spleen extended a handsbreadth below ribs and her liver edge almost to the umbilical level. No ascites. No petechiæ. Blood studies: red cells, 3,000,000; white cells, 5500; hemoglobin, 34 per cent. Polymorphonuclear neutrophils, 64 per cent; lymphocytes, 33 per cent; monocytes, 2 per cent; eosinophils, 2 per cent. Marked poikilocytosis and anisocytosis and slight polychromatophilia. Platelets, 200,000 per cc. Bleeding time and coagulation, normal. Blood Wassermann, negative. Reticulocytes, 1.5 per cent.

Dr. Houser cauterized intranasal telangiectases. In view of previous experiences in another city with severe transfusion reactions which made her "sick with jaundice," the patient was much averse to receiving any more. For this reason our record unfortunately contains no "blood typing" report. Attempts to get further information from the patient recently have been unavailing.

Summary Comment, Case IV. Here, too, we see the combination of hereditary hemorrhagic telangiectasia with severe anemia (apparently out of proportion to bloodloss), enlargement of spleen and liver and a history of serious intolerance to blood transfusion. I have examined one son of this patient who is now thirty-five years of age and who has suffered violent epistaxis but whose blood level is normal and whose liver and spleen are not palpable. Dr. Houser has carefully and repeatedly cauterized this young man's intranasal lesion so that epistaxis has ceased for the past year.

The literature of hereditary hemorrhagic telangiectasia is for the most part devoid of reference to splenomegaly and to transfusion intolerance and to blood grouping. The author's case reported in 1923 (incidentally in no way related to the 4 patients of the present study) was described as having an "easily palpable spleen." The review made at that time disclosed no similar findings in other reported cases. Recently, Dr. H. I. Goldstein, of Camden, New Jersey, very kindly placed at the author's disposal his comprehensive bibliography of hereditary hemorrhagic telangiectasia and of hereditary epistaxis. Dr. Goldstein (personal communication) had not himself observed splenomegaly in cases reported by him[3] but was aware of the case of M. G.[1] herein reported and further called the author's attention to reports by Roles[4] and Curshmann,[5]

each of whom mentioned a case of splenomegaly in this disease. In addition to these the author has found only two other references germane to the subject, one of Symmers[6] and one of Schoen.[7]

Epitome of Cases of Hereditary Hemorrhagic Telangiectasia with Splenomegaly Reported in the Literature. 1. Roles' Case:[4] A woman, aged sixty-five years, had been previously treated for cirrhosis of the liver and thrombophlebitis of the left leg. She was found to have multiple telangiectases of pin-point, spider form, and nodular types, scattered over her face, nose, lips, tongue, cheeks and hands. The spleen was firm, nontender, extended well below the ribs (the "size of an orange") and had a "well-marked notch." Blood count was normal—as was coagulation time. No blood type determination was made and of course no blood transfusion was given. The report states that the patient had epistaxis for two months but no family history of epistaxis or telangiectases was obtained. This is apparently an atavistic example of hereditary hemorrhagic telangiectasia with splenomegaly—although one cannot exclude ordinary atrophic cirrhosis of the liver with acquired telangiectases. The liver findings are not mentioned.

2. Curshmann's Case.[5] A man, aged fifty-four years, with classical personal and family history of the disease was reported as having liver enlarged two fingers below ribs, and spleen "easily palpable." Blood count normal. No blood-type determination made.

3. Symmers' Cases[6] are reports of hemangioma of the spleen and have no personal or family histories in any way suggesting that they belong in the group under discussion.

4. Schoen's Case[7] is the first in his series and the only one with splenomegaly. (Schoen presents a most excellent review of the disease in general.) Herr S. S., aged fifty-six years, had typical personal and family history and typical telangiectases. His spleen was "eben fühlbar." His blood count was: reds, 1,900,000; whites, 9800; hemoglobin, 25 per cent. His blood was of Group 0 (Type IV, Moss). He was given two transfusions, in spite of "schockerscheinungen." This case is particularly interesting because, like the author's cases, it too belonged to Type IV and presented evidence of intolerance to blood transfusion.

Discussion. The incidence of splenic and hepatic enlargement in hereditary hemorrhagic telangiectasia is probably not great—otherwise it would have been emphasized before. The author's experience, small though it is, would incline toward the belief that these enlargements occur relatively late in the disease and only in the more severe cases. The author has not encountered splenomegaly in the youthful sufferers or in the nonafflicted members of families with this disease. It must also be admitted that severe cases of the disease occur without discoverable splenomegaly.

If we admit that the splenic and hepatic enlargement in the 4 cases reported above is more than a merely accidental and unrelated finding, we then have to consider the following possibilities: is the liver-spleen enlargement simply a reactionary and compensatory hypertrophy caused by repeated losses of blood over many years? Or is it indicative of a more fundamental disorder of these organs—at first "latent" and finally in certain severe cases manifest—constituting an integral part of the constitutional pathology of hereditary hemorrhagic telangiectasia itself?

The problem cannot be solved by the data at hand. Chronic secondary posthemorrhagic anemias, as in cases of fibroma uteri, peptic ulcer, hemorrhoids, and so forth, rarely, if ever, are associated with splenomegaly. A condition designated as "myelophythisic splenomegaly" has been reported by Ballin and Morse,[8] but a critical view of their cases leaves one with the impression that aleukemic leukemia cannot be excluded. Certainly the blood pictures of our cases of hemorrhagic telangiectasia are not suggestive of myelophthisic anemia or of aplastic anemia (see "plastic" blood pictures described in all 4 cases as well as bone marrow in Case I).

The transfusion intolerance, so clearly indicated in these cases, is reported without attempt at explanation except to suggest that the preëxisting liver-spleen disorder may be the underlying cause. The posttransfusion jaundice which developed in Case I was clearly obstructive (due to hepatitis) and not hemolytic in type.

The identity of blood group (0) in these cases of hereditary hemorrhagic telangiectasia with splenomegaly may be nothing more than a coincidence—as this blood group comprises a little less than half of all human beings. It is reported, however, so that its significance, if any, may be determined by other workers. It is barely possible that blood Group 0 is also an integral part of the constitutional hereditary background of this particular splenomegalic type of hereditary hemorrhagic telangiectasia. I am informed of one case of hereditary hemorrhagic telangiectasia *without splenomegaly* whose blood was Type II, Moss (Dr. H. I. Goldstein and Dr. S. Barbash).

Summary. Four cases of hereditary hemorrhagic telangiectasia are reported exhibiting the following noteworthy features:

1. Splenomegaly and hepatic enlargement.
2. Increasing intolerance to blood transfusion resulting in posttransfusion jaundice (and death in two).
3. The coincidence of identical blood group (0) in all of those tested who presented the splenomegalic syndrome.

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REVIEWS.

WILLIAM STEWART HALSTED, SURGEON. By W. G. MACCALLUM. Introduction by DR. W. H. WELCH. Pp. 240; 18 illustrations. Baltimore: The Johns Hopkins Press, 1930. Price, $2.75.

ANOTHER of Johns Hopkins' great original medical faculty of four has now received sympathetic and adequate consideration by his biographer. A more difficult task than in the case of Osler, whose wider spreading temperament and achievement made him an easier subject for portrayal, it has been equally well and perhaps even more artistically presented by Dr. Halsted's "pupil, colleague and friend of many years." When anyone with the wide contacts and experience of Dr. Welch says, as he does in his entertaining Introduction, that "no one did more by precept and by example to secure the triumph of antiseptic surgery in America than Halsted and certainly no one has done more to improve still further methods of wound treatment," it indeed behooves us to learn what we can about such an important figure in American surgery and medical education. We might sincerely regret, therefore, that the author has not seen fit to go into further details of such an interesting life; long periods and phases being sometimes scantily dismissed or completely omitted. On second thought, however, one realizes that the peculiar charm of Dr. MacCallum's writings is that he limits himself to what he knows at first hand, and this he portrays accurately and *con amore*. After literally years of familiarizing himself with an already well-known series of events, he has told a good story, which doubtless contents him and should satisfy all but the gluttonous reader. We learn how Halsted's natural surgical brilliancy and dexterity was consciously replaced by him with more plodding but thorough and safer methods that were more in keeping with modern advances and permitted a more scientific method of study of surgical problems. His lasting interest in the problems of wound healing, in which field, according to Welch, lie his most important contributions, crops up throughout the story; and the tale of the triumphs and dangers of the anesthetic effects of cocaine is wisely and instructively told.

Halsted's "intriguing" but in some ways difficult personality is well summarized in the Introduction, but forms itself even more substantially as the narrative proceeds. His aloofness, tendency to shrink from publicity, "absolute indifference in the assertion of prior claims," and details of personal appearance gradually give place in the readers' attention to the more elusive but more essential

qualities of kindliness, generosity and true philanthropy that were doubtless adequately known only to the chosen few.

As we would like to keep the book on our shelves for biographical reference, after having read the entertaining story, we regret the absence of an index, and hope that the author will not resist advice to include the one already prepared in the new edition which we understand is soon to be forthcoming. E. K.

OXFORD MONOGRAPHS ON DIAGNOSIS AND TREATMENT. Edited by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Hersey Professor of the Theory and Practice of Physics, Harvard University. Ten volumes (nine of which have appeared). New York: Oxford University Press, 1928–1930. Price, $100.00 set of 10 volumes.

IN his "Foreword" to this excellent series of volumes, Doctor Christian has stated its purpose in part in these words: "To the man who practices medicine two questions arise with great frequency: what is the matter with my patient, and how shall I treat his ills? . . . . . In the modern era of medicine very striking advances have been made in methods of diagnosis . . . . . The good diagnostician of today must know more facts, understand the use of more methods than was true of former generations of medical men. . . . . There has come a present period of medicine in which treatment in all of its forms occupies possibly a larger place in medical literature than any phase of medicine. With so much known of diagnosis and treatments, and with so many things being steadily added by medical investigators, there is a real need among those who practice medicine for comprehensive discussions of diagnosis and treatment by men competent to select what is best, and to present it with sufficient detail and clarity for it to be of practical help in the problems of practice. For this purpose this series of 'Monographs on Diagnosis and Treatment,' has been prepared. Each volume is a complete discussion of the diagnosis and treatment of a certain group of diseases written by one author."

The whole idea is an excellent one, and it has been very satisfactorily carried out. The writers of the individual monographs have been well selected and their presentations are of a high degree of excellence. They have, for the most part, carefully adhered to the plan of a complete discussion of diagnosis (including pertinent clinical data and special diagnostic procedures) and the details of treatment, with only the briefest incidental mention of etiology and pathology. The work is therefore eminently suited to the practitioner with "some considerable clinical experience." It covers a wide range of subjects which have been well selected with the needs of the practitioner in view, subjects our information concerning which has been particularly enlarged and revised in recent years.

The books themselves are a triumph of the bookmaker's art. The loose-leaf form has been adopted, making possible revisions and additions as new knowledge is available. The binding mechanism is the simplest and at the same time the most effective that has come to our notice: it can be opened and closed quickly, without the use of key, etc., and has an expansion possibility of 50 per cent. The type is large and clear, the lines wide-spaced; the volumes of a handy size and altogether pleasing; the illustrations, especially Roentgen ray films, exceedingly well done.

It is, perhaps, to be regretted that such an expensive format was used, for the work deserves the widest distribution among practitioners. As the volumes cannot be purchased singly, it means an initial outlay of one hundred dollars, a prohibitive sum for many. The costliness of the work may be realized from this comparison: the nine volumes now in print contain about 1,000,000 words of text (for ninety dollars); a popular one-volume text-book of medicine contains some 900,000 words of text (for nine dollars). It is at least to be hoped that the cost of future revision and addition sheets will not be as expensive as has been the case in certain other loose-leaf medical publications whose plan of action seems to have been to "catch subscribers first," and then to charge outrageously for subsequent material.

Vol. I. The Diagnosis and Treatment of Disorders of Metabolism, by James S. McLester, M.D., Professor of Medicine, University of Alabama. Pp. 328; 6 illustrations.

The opening chapter deals with normal metabolism, including also nutritive requirements, and the determination of the basal metabolic rate. Then follow chapters on disorders of intermediary metabolism (alkaptonuria, cystinuria, phosphaturia, oxaluria and uraturia), disturbances of water balance (anhydremia, edema, diabetes insipidus) and disturbances of acid-base equilibrium. The larger part of the volume is devoted to gout, obesity and diabetes mellitus, with a short concluding chapter on pentosuria and hemachromatosis. Dr. McLester has handled difficult subjects exceedingly well: he has given the practitioner an adequate and intelligible presentation and at the same time has avoided unnecessary and confusing details. The Reviewer feels, however, that more should have been said about renal glycosuria; that the condemnation of "diabetic foods" is too sweeping; that the work of Evans on obesity might have been referred to with advantage.

Vol. II. The Diagnosis and Treatment of Diseases of the Stomach and Intestines, by William Fitch Cheney, B.L., M.D., Clinical Professor of Medicine, Stanford University. Pp. 280.

Part I, devoted to diseases of the stomach, includes chapters on acute and chronic gastritis, gastric ulcer, cancer, syphilis of the

stomach, gastroptosis, and the gastric symptoms due to appendix, gall-bladder and liver disease (cirrhosis, syphilis and cancer). Part II describes the inflammations of the intestines (acute enteritis, enterocolitis and colitis; chronic catarrhal colitis; chronic mucous colitis; chronic ulcerative colitis, which is considered as of four types—due to the tubercle bacillus, to Amœba histolytica, to the Shiga bacillus, and to the Diplobacillus of Bargen); cancer; acute intestinal obstruction; chronic intestinal stasis; tapeworm; acute and chronic appendicitis. The book is well written and in an interesting style. The presentation is, however, not as complete as might have been expected in such a monograph: for instance, one might hope for a clearer statement of surgical indications in ulcer treatment, some reference to postoperative treatment of ulcer cases, to marginal ulcer. No mention is made of diverticulitis. While the organism of Bargen is given as the etiologic factor in ulcerative colitis not due to amebæ, or to the Koch or the Shiga bacillus, no mention is made of the possible allergic factor in mucous colitis. The Reviewer is not convinced that hemoglobin and red cell estimations immediately after massive ulcer hemorrhage will reflect the degree of blood loss, or that a "Babinsky" reflex is to be expected in tabes dorsalis. A number of medicaments not listed in "New and Non-official Remedies" are advised.

VOL. III. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE HEART, by HENRY A. CHRISTIAN, M.D., Sc.D., LL.D. Pp. 355.

There are chapters on acute endocarditis, acute myocarditis, acute and chronic pericarditis, chronic cardiac valvular disease, chronic myocardial disease, syphilis of the aorta, angina pectoris, cardiac infarction, the cardiac disturbances of thyroid disease, certain of the arrhythmias, cardiac neuroses, and congenital heart lesions. The author's years of experience as physician, consultant and teacher, his superlative ability to express himself, and, above all, his good judgment combine to make this volume a masterpiece. There is just the right emphasis, the proper proportion and balance of material. Every practitioner and every senior medical student should read and reread the introductory chapter and the section on digitalis.

VOL. IV. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE THYROID, by JAMES H. MEANS, M.D., Jackson Professor of Clinical Medicine, Harvard University, and EDWARD P. RICHARDSON, M.D., John Homans, Professor of Surgery, Harvard University. Pp. 366; 50 illustrations.

The opening chapter, historical in nature, outlines the development of our knowledge of the thyroid; the second discusses the functions and diseases of the thyroid from the standpoint of normal

and pathological physiology; the third chapter is devoted to the principles underlying the diagnosis and treatment of thyroid disease. Then follow chapters on colloid goiter, exophthalmic goiter, adenomatous goiter, myxedema and cretinism, and malignant tumors and inflammations of the thyroid. The authors have departed from the general plan of discussing chiefly diagnosis and treatment, as used in the other volumes of the series, and rightly so: much of our knowledge concerning the thyroid is still very recent in origin, and in part, at least, controversial. They give a very complete presentation, including the history of our knowledge of thyroid diseases, the physiology and pathology of the gland, the newer knowledge concerning thyroid anatomy (illustrations of Wilson's wax reconstructions) as well as the clinical pictures and therapeutic measures. Numerous well-selected case reports are cited to illustrate points under discussion. To each chapter is appended a considerable bibliography. The style is clear and convincing. Their opinions are largely in accord with those held in most thyroid clinics, except, perhaps, what might be called their underestimation of the value of Roentgen therapy.

Vol. V. The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract, by Elmer H. Funk, M.D., Clinical Professor of Medicine and Therapeutics, Jefferson Medical College. Pp. 618; 150 illustrations.

Part I (89 pages) describes the essentials of the diagnostic and therapeutic methods applicable in diseases of the lower respiratory tract. In Part II are considered diseases of the trachea, bronchi and lungs: the various types of bronchitis; bronchiectasis; bronchial obstruction; foreign bodies in trachea and bronchi; broncholithiasis; pulmonary congestion and edema; emphysema; atelectasis; abscess; gangrene; bronchopulmonary spirochetosis; pulmonary fibrosis; pneumoconiosis; pulmonary syphilis; the pulmonary mycoses; parasitic diseases; pulmonary embolism, thrombosis and infarction; pulmonary arteriosclerosis; hemoptysis; hernia of the lung. Part III deals with the diseases of the pleura. In Part IV are discussed pulmonary tuberculosis, intrathoracic newgrowths and diseases of the diaphragm. The subject matter is well presented. Of particular merit are the sections on foreign bodies in the trachea and bronchi; pneumoconiosis, pulmonary tuberculosis and intrathoracic newgrowths. There are numerous illustrations, especially roentgenograms which are exceedingly well reproduced.

Vol. VI. The Diagnosis and Treatment of Arthritis, by Russell L. Cecil, M.D., Sc.D., Assistant Professor of Clinical Medicine, Cornell University. Pp. 216; 14 illustrations.

Part I deals with acute arthritis. This is considered under these headings: (*a*) infectious arthritis (rheumatic fever); (*b*) septic

arthritis (gonococcal arthritis, pneumococcal arthritis, suppurative arthritis, and other less common forms of acute bacterial infection of the joints); (*c*) noninfectious arthritis (allergic arthritis, intermittent hydrarthrosis and traumatic arthritis). Part II takes up chronic arthritis which is classified as (*a*) infectious arthritis, including (1) specific forms (syphilitic and tuberculous arthritis) and (2) chronic infectious arthritis (arthritis deformans or rheumatoid arthritis; Still's disease); (*b*) degenerative arthritis (hypertrophic arthritis, degenerative monarticular arthritis, Heberden's nodes, climacteric arthritis, senile arthritis and the Charcot joint); and (*c*) metabolic arthritis (gout), with concluding chapters on mixed forms of chronic arthritis and on spondylitis. The classification is sound and practical and will be found most helpful by all readers. The several clinical pictures are well described and the problems of differential diagnosis are fully presented. The voluminous and confusing literature on the subject has been judiciously evaluated. The principles and details of treatment, including their limitations, are clearly stated.

VOL. VII. THE DIAGNOSIS AND TREATMENT OF VARIATIONS IN BLOOD PRESSURE AND NEPHRITIS, by HERMAN O. MOSENTHAL, M.D., Professor of Medicine and Attending Physician, New York Post-Graduate Medical School and Hospital. Pp. 184.

This volume is as yet incomplete, Part II (nephritis) not having appeared. Part I deals with variations in blood pressure. There are chapters on physiologic dynamics controlling arterial pressure; normal arterial pressure; clinical methods of estimating blood pressure (with a section on the recording sphygmomanometer by Daniel R. Barr); capillary and venous pressure, and hypotension (section on capillary pressure written by Ernst P. Boas); tests of functional efficiency of the circulation (description of their respective functional efficiency tests by C. Ward Crampton, Edward C. Schneider and Harold M. Frost); blood pressure as related to life insurance (by Harold M. Frost); the influence of habits and daily routine upon blood pressure; types of increased blood pressure; essential hypertension. While the author has limited his material to what he considers practical for the reader, he has given an adequate statement of views of others in a field where many and varied beliefs are current. Should the reader wish to investigate further, he is furnished with nearly 250 references to the literature.

VOL. VIII. THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE LIVER AND BILIARY TRACT, by JOHN PHILLIPS, M.B., Chief of Medical Division, The Cleveland Clinic. Pp. 539; 58 illustrations.

Part I takes up the embryology, gross anatomy and the physiology of the liver, its congenital and acquired deformities and displacements, the methods of examination and liver function tests.

Part II deals with the diseases of the liver itself. Part III with those of the extrahepatic bile ducts, and Part IV with the diseases of the gall bladder. This volume, while giving a good description of the clinical picture and treatment of the various diseases of the biliary system, should be particularly valuable to the practitioner because of its clear and concise presentation of our newer knowledge of liver function, of the tests for liver function and jaundiced states (especially the van den Bergh and dye elimination tests) and cholecystography. The section on hemolytic jaundice might have been shorter, since the condition is rightly and fully described in the volume on the diseases of the blood. The volume is exceedingly well written; the illustrations well chosen and reproduced. Medicine indeed suffered a great loss in the tragic and untimely death of Doctor Phillips, very shortly after the completion of this manuscript, in the Cleveland Clinic disaster.

Vol. IX. The Diagnosis and Treatment of Diseases of the Blood, by Thomas Ordway, M.D., Dean and Associate Professor of Medicine, Albany Medical College, and L. Whittington Gorham, M.D., Clinical Professor of Medicine, Albany Medical College. Pp. 605; 33 illustrations.

After a discussion of the formed elements of the blood follow chapters on pernicious anemia, chlorosis, sickle-cell anemia, hemolytic jaundice, anemia due to hemorrhage and to infection, granulocytopenia, aplastic anemia, anemia of pregnancy, anemia associated with systemic diseases, the leukemias, acute infectious mononucleosis, polycythemia, the purpuras, hemophilia, hemorrhage of the newborn, and a concluding chapter on the anemias of childhood written by Kenneth D. Blackfan, M.D., professor of pediatrics at the Harvard Medical School, and his associates, James M. Baty, M.D., and L. K. Diamond, M.D. From the practitioner's standpoint, this is the best book on hematology which the Reviewer has encountered. The descriptions are clear, concise and accurate, with numerous illustrative case reports, and many well selected references to the literature. The style is excellent. The illustrations are well done. So rapid have been the advances that the present conception of granulocytopenia has completely changed since the book was written. It is to be hoped that in their revision, the authors will prefer the term granulocytopenia to the inaccurate agranulocytosis (literally, a lack of an increase of granulocytes).

R. K.

Intestinal Toxemia. Biologically Considered. By Anthony Bassler, M.D., F.A.C.P. Pp. 433; 16 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $6.00.

This book represents biased but poor writing by an enthusiast who makes many inexcusable statements and fails to throw any light on the obscure subject he treats.

F. L.

A Textbook of Medicine. By Russell L. Cecil, A.B., M.D., Sc.D. Associate Editor for Diseases of the Nervous System, Foster Kennedy, M.D., F.R.S.E. Pp. 1592. Second edition. Philadelphia: W. B. Saunders Company, 1930. Price, $9.00.

That a second edition of this work should be necessary within four years is a sufficient recommendation of its soundness. As the editor points out in the preface to the first edition, the rapid growth of medical science during recent years has made it almost impossible for a single individual to master the entire field. This book, therefore, is the coöperative effort of over 130 contributors, each of whom is a student or investigator of the subject upon which he has written. In the new edition there are several changes in the list of contributors due to loss by death among the original writers, and several new names appear as authors of new chapters. Even a casual comparison of the present volume with its predecessor, shows plainly the extensive and often radical changes that have been made by the various contributors in the treatment of their subjects.

The Reviewer is in hearty accord with the editor's prophesy; "that it is doubtful whether any author of the future will have the temerity to write a complete textbook on medicine without considerable collaboration."

Indeed it is to be hoped that the success of this splendid treatise will lead to the production of other authoritative works built upon the same plan. B. L.

A Brief History of Medicine in Massachusetts. By Henry R. Viets, M.D. Pp. 194; 8 illustrations. Boston: Houghton Mifflin Company, 1930.

Written as a "contribution by the Massachusetts Medical Society to the Tercentenary Celebration of the Massachusetts Bay Colony," this book covers entertainingly the more important phases of Massachusetts' (really Boston's) medical history. Though mostly of local interest, the argument at times—such as the discovery of ether anesthesia and Minot's dietary treatment of pernicious anemia—attains world importance. In the anesthesia story, "credit for introducing surgical anesthesia to the world" is given to Morton, though Long receives (in Welch's words) "the credit of independent and prior experiment and discovery." Who shall say which is the greater contribution?

Following a chapter on the preacher-physicians and the apprentice system, come the interesting eighteenth controversy on inoculation and word pictures of such well-known early figures as the two Warrens, Waterhouse, Douglass and James Lloyd. The divided

patriotic feelings during the Revolution—even in that hotbed of patriotism—and the conditions leading to the foundation of the Harvard Medical School, the Massachusetts General Hospital and the Massachusetts Medical Society receive sympathetic attention, also the five medical families—the Warrens, Jacksons, Bigelows, Bowditches and Shattucks.

The work should have a far wider appeal than to the New Englanders whom it chiefly concerns. E. K.

LEGAL MEDICINE AND TOXICOLOGY. By RALPH W. WEBSTER, M.D., PH.D. Pp. 862; 47 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $8.50.

WHILE most phases of American medicine are oversupplied with textbooks of conventional scope and treatment, this is distinctly not so in the field of Toxicology and Legal Medicine. Webster's book, therefore, is welcome for this reason, as well as because it presents a wealth of valuable material from an acknowledged authority. Almost twice as much space is devoted in it to Toxicology as to Legal Medicine. This permits a fairly constant consideration of mode of action, symptoms, fatal dose, treatment, postmortem appearance, methods of detection of most of the substances important in toxicology. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Medical Clinics of North America (Mayo Clinic Number—November, 1930). Pp. 261; 50 illustrations. Philadelphia: W. B. Saunders Company.

Progressive Medicine, Vol. IV. December, 1930. Edited by HOBART AMORY HARE, M.D., LL.D., assisted by LEIGHTON F. APPLEMAN, M.D. Pp. 383; 75 illustrations. Philadelphia: Lea & Febiger, 1930.

The Population Census of 1930. Pp. 33. LOS ANGELES CHAMBER OF COMMERCE.

Die Grundlagen der Religionsphilosophie (Nomotheismus). By TH. ZIEHEN. Pp. 164. Leipsig: Felix Meiner, 1928. Price, RM. 3.80.

A history and critique of interpretations of the chief religio-philosophic systems. Of indirect medical interest only.

Bright's Disease. Observations on the Courses of Different Types and on the Resultant Changes in Renal Anatomy. By D. D. VAN SLYKE, EDGAR STILLMAN, EGGERT MÖLLER, W. EHRICH, J. F. MCINTOSH, L. LEITER, E. M. MACKAY, R. R. HANNON, N. S. MOORE, and CHRISTOPHER JOHNSTON. Pp. 130; 41 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, $3.00.

The Morphine Habit and Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (Oxon.). Pp. 94. London: H. K. Lewis & Co., Ltd. Price, 5/, net.

An optimistic treatment of the morphine habit with emphasis on the avoidance of "withdrawal shock."

Microbiology and Elementary Pathology. By CHARLES G. SINCLAIR, B.S., M.D. Pp. 362; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $2.50.

Miscellaneous Contributions on the Costs of Medical Care. Number 5. The Use of Small Loans for Medical Expenses. By LEON HENDERSON. Pp. 10. Washington, D. C.: The Committee on the Cost of Medical Care.

Miscellaneous Contributions on the Costs of Medical Care. Number 6. The Cancer Program of Massachusetts. By GEORGE H. BIGELOW, M.D. Pp. 8. Washington, D. C.: The Committee on the Cost of Medical Care.

The Surgical Clinics of North America, Vol. 10—No. 6 (Philadelphia Number —December, 1930). Pp. 316; 95 illustrations. Philadelphia: W. B. Saunders Company.

William Stewart Halsted, Surgeon. By W. G. MACCALLUM. Introduction by DR. W. H. WELCH. Pp. 240; 18 illustrations. Baltimore: The Johns Hopkins Press, 1930. Price, $2.75.

Saint Bartholomew's Hospital Reports, Vol. LXIII. Edited by SIR THOMAS HORDER, BART., K.C.V.O., *et al.* Pp. 272; illustrated. Supplementary Volume. *Deep X-ray Therapy in Malignant Disease.* By WALTER M. LEVITT, M.B., D.M.R.E., with an introduction by SIR THOMAS HORDER, BART., K.C.V.O., M.D., F.R.C.P. Pp. 128; 10 illustrations. London: John Murray, 1930.

This valuable series of hospital reports contains articles by such well-known men as Horder, Francis Fraser, Wilfrid Shaw, Richard Armstrong and others.

Treatment of Epilepsy. By FRITZ B. TALBOT, M.D. Pp. 308; 11 illustrations. New York: The Macmillan Company, 1930. Price, $4.00.

Chronic Arthritis and Rheumatoid Affections with Recovery Record. By BERNARD LANGDON WYATT, M.D., F.A.C.P., with the collaboration of LOUIS I. DUBLIN, PH.D., and Foreword by DR. J. VAN BREEMEN. Pp. 141. New York: William Wood & Co., 1930. Price, $2.50.

Industrial Microbiology. By HENRY FIELD SMYTH, M.D., DR. P.H., and WALTER LORD OBOLD, M.S. Pp. 313; illustrated. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.00.

Carnegie Institution of Washington Publication No. 411. Leonardo da Vinci, The Anatomist, 1452–1519. By J. PLAYFAIR MCMURRICH, with a Preface by GEORGE SARTON. Pp. 262; 89 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, $6.00.

NEW EDITIONS.

Medizinal-Index, Teile I and II. By DR. M. T. SCHNIRER. Pp. 224. 31st Edition. Leipsig and Wien: Franz Deuticke, 1931. Price, M. 4.60.

A compact but necessarily fragmentary compend covering recent developments in therapeutics, infant feeding, new expressions, and so forth, of more use to German and Austrian physicians than in this country.

Text-book for Nurses. Surgical and Medical. By E. W. HEY GROVES, M.D., B.SC., M.S., F.R.C.S., Surgeon to the Bristol General Hospital, and The Late J. M. FORTESCUE-BRICKDALE, M.A., M.D. (Oxon.), M.R.C.P. (Lond.), Senior Assistant Physician, Bristol Royal Infirmary. The Medical Section revised by J. A. NIXON, C.M.G., M.D. (Cantab.), F.R.C.P. (Lond.), Professor of Medicine and Director of Clinical Medicine in the University of Bristol.

One of the best of books of its kind that we have seen.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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A Comparative Study of Hemolytic Streptococci from Patients Convalescent from Scarlet Fever.—It is obvious that the control of scarlatina may depend upon measures taken to prevent transmission of the specific streptococcus from man to man. KIRKBRIDE, WHEELER and WEST (*J. Infect. Dis.*, 1930, **47**, 16) investigated 85 cases of scarlet fever in order to determine whether the type of hemolytic streptococci present at the onset of the infection change during the course of the disease and "whether any relationship could be established between the reactions of a particular strain and the epidemiologic evidence of its ability to induce infections in human beings." From 50 to 60 per cent of the patients discharged at the end of the thirty-day quarantine had hemolytic streptococci in their nasopharyngeal secretions. Only 6 per cent of 34 patients who were carriers of this streptococcus could be incriminated as a possible source of scarlatina which occurred in individuals with whom they came in contact. The strains that were isolated showed marked variations in their cultural, biochemic and serologic characteristics, but there was no fundamental difference between the organisms cultured at the beginning of the disease and long after convalescence had occurred nor could any differences be found that bore relation to the infectivity of the strain at the time of isolation.

Undulant Fever (Brucelliasis).—The occurrence of a considerable number of new cases of undulant fever in the community from which this abstract is written makes particularly appropriate for review this article on a clinicopathologic study of 90 cases as reported by SIMPSON (*Ann. Inter. Med.*, 1930, **4**, 238). He writes that the disease is rapidly increasing throughout the United States or else the disease is being recognized more generally than it has been in the past. For example, prior to 1925 only 128 cases had been reported in this country, whereas in the year 1929, 1301 cases alone were reported and from every state in the Union. Undulant fever may be caused by the Bacillus abortus

of Bang or the Micrococcus melitensis of Bruce. The two organisms are remarkably similar, so much so that it is customary to refer to them as the abortus-melitensis group of organisms, and the generic name, Brucella, has been used to designate the several types of organisms belonging to this group. The organism in the majority of instances is transmitted to the human being as a result of the drinking of raw milk or consuming unpasteurized dairy products, although it is possible that the organism may enter through the skin. Brucella abortus infection in cattle is widely disseminated throughout this country and it is undoubtedly from these cattle that the disease is transmitted to the human. In man the clinical expressions of brucelliasis are by no means clear-cut. It is only after a continued febrile course without any explicable origin that the possibility of Brucella infection is considered. Simpson believes, however, that the disease is sufficiently characteristic to enable the discerning physician to make the diagnosis without much difficulty. Following the initial prodrome there occur fever, chills and sweats. The most characteristic feature of the fever is the general feeling of well being that the patient notices despite a temperature as high as 102° to 103° F. This is usually an afternoon rise of temperature, the morning hours showing a marked remission or intermission. The sweats are extremely common and quite characteristic, occurring during the early morning hours and often of a severe drenching character. The pulse is characteristically slow. Sleep is disturbed by the sweats, but on the whole the average patient gets along very well. A febrile course persists from one week to several months, with an average duration of about four months. There is a total absence of physical findings or at least physical findings which would indicate the disorder. Brucella abortus shows the same predilection for the genital tract of human beings as it does in susceptible animals. The disease may produce human abortion and in man occasions various complications in the genital tract. The diagnosis is confirmed by the agglutination reaction. The agglutinins appear usually during the second week and persist for variable times, possibly many years after the subsidence of the attack. Blood cultures and urine cultures, animal inoculations and skin tests may also be used to substantiate clinical diagnosis. Prophylaxis of the disease is extremely important. There is a basic need for strict supervision of pasteurization processes. Active treatment with chemicals has been unavailing. In 46 of Simpson's cases a vaccine made from heat-killed Brucella abortus apparently was decidedly efficacious.

SURGERY

UNDER THE CHARGE OF

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The Anatomical Result of Periarterial Sympathectomy. — Blair, Doff and Bingham (*Brit. J. Surg.*, 1930, **18**, 215) claim that the condition of the nerves in the main arteries was investigated in a leg ampu-

tated five weeks after the periarterial injection of alcohol into the sheath of the femoral artery. All nerves running with the artery at the seat of the previous operation appeared to have degenerated distally, but an abundant additional supply was discovered running to the vessels lower down from the ordinary nerves of the limbs that showed up in marked contrast. This accessory nerve supply arrives upon the vessels of the leg mainly in the popliteal space. The incidence of these accessory nerves was also checked by anatomical dissection in another limb. The incoming nerve twigs have a characteristic structure, being composed chiefly of small medullated fibers, with a few large medullated fibers and a fair number of nonmedullated fibers. It is suggested that these incoming nerves may be specially concerned with the bloodvessels to the muscles.

The Mixed Tumors of the Salivary Glands.—PETTY (*Brit. J. Surg.*, 1930, **18**, 241) says that as a result of the present study the conclusion has been reached that the mixed tumors of the salivary glands are a composite group of epithelial tumors, the varying pathologic features of which depend on the degree of differentiation attained, the rapidity of division of the cells and the amount of myxomatous change undergone by the epithelium; according to the degree to which these changes have taken place, all gradations may be encountered between a myxoma on the one hand and a highly differentiated tumor with ducts and acini on the other; and between a slowly growing tumor with regular cells and an irregular anaplastic growth. Based on these factors a practical pathologic classification has been evolved. The combined pathologic and clinical study has shown that this classification allows of a certain amount of correlation between the clinical and pathologic findings, but that the correlation is by no means complete.

Indications and Contraindications for Nephrectomy in Renal Tuberculosis.—SPITZER (*J. Urol.*, 1930, **24**, 469) declares that the absence of tubercle bacilli in the secretion from a kidney, does not mean that tuberculosis of such kidney does not exist. The presence of tubercle bacilli in the urine means that a focus of tuberculosis is present either in the genital or the urinary tract somewhere as the tubercle bacilli do not pass through normal epithelium anywhere in the body. The presence of pus from a supposedly well kidney does not condemn such kidney in the presence of a known tuberculous kidney on the opposite side. It must not be forgotten that pus in a segregated urine may result from other conditions than tuberculosis. There are three types of tuberculosis of the kidney, the ulcerocavernous type being the only one with which the urologist concerns himself. Years of experience, as testified to by careful observers have demonstrated that patients suffering from tuberculosis of the kidney, have a better chance of recovery from other conditions, whether they be tuberculous or not, when such diseased kidney is removed. Progressive ill health and eventually death are the rule with occasional exceptions, where tuberculosis of the kidney cannot be treated by nephrectomy and the reverse is true where it is possible and wise to practice nephrectomy.

THERAPEUTICS

UNDER THE CHARGE OF

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The Influence of Standardized Extracts of Thymus and of Spleen on Basal Metabolism.—SCHNEIDER and NITSCHKE (*Klin. Wchnschr.*, 1930, **9**, 1489) report the results of careful investigation of a new extract prepared from the thymus or from the spleen by means of acetic alcohol and ether. These extracts are standardized on rabbits by their ability to reduce the content of inorganic phosphorus in the blood serum, one unit being 0.1 of that amount capable of causing a 50 per cent reduction of blood serum phosphorus in a rabbit weighing 2 kg. within a period of twenty-four hours. With these new extracts they have reinvestigated the question of whether or not basal metabolism is influenced by the spleen or the thymus a problem, the investigation of which has in the past yielded highly discordant results. With these new extracts they find that the subcutaneous injection of from 1 to 2 units reduces the basal metabolism of test animals within a period of six to twelve hours and that the maximum reduction appears at the end of about twenty-four hours. The degree of reduction averages about 23 per cent. Larger doses fail to produce a greater degree of reduction. The extracts are also capable of producing a similar reduction in animals the basal metabolism of which has previously been raised by the injection of thyroxin. In fact, it is possible by the use of these extracts completely to counteract the metabolic effects of thyroxin. Extracts prepared in a similar manner from other portions of the lymphatic system exert a similar action upon basal metabolism. Like extracts prepared from liver and muscle have no effect. The nature of the active substance in these extracts of thymus and spleen is not yet determined, but they are virtually free from protein and fat. They vary in their content of inorganic salts, some being poor and others rich but this difference in extracts seems to be without influence upon their activity. It seems possible that the active substance is in the nature of a hormone. The therapeutic value of these extracts in man cannot yet be stated.

The Treatment of Postencephalitic Manifestations with Harmin Alkaloid.—FRANK and SCHLESINGER (*Klin. Wchnschr.*, 1930, **9**, 1864) tested the beneficial effect of the alkaloid harmin alone or in combination with scopolamin on 12 cases with postencephalitis and 2 cases of paralysis agitans. After a critical analysis of the possible spontaneous variations in the clinical condition of the patients, the authors con-

cluded that in 4 patients the improvement was marked; in 4 patients, satisfactory; and in 2, only slight. In 2 cases no change in the clinical condition was observed. It is of interest that in these 2 cases no beneficial response was noted after the administration of scopolamin. The effects of harmin were apparent fifteen minutes after subcutaneous injection and twenty minutes after per oral administration. The duration of the effect of harmin varied from three hours to four days. The doses of single injections varied from 0.015 gm. to 0.05 gm. Harmin therapy in keratin capsules also proved efficacious after per oral administration. If the single doses reached 0.06 gm. toxic manifestations such as dizziness, nausea, headache, restlessness and collapse developed. The therapeutic effect of harmin was most pronounced on the voluntary movements. The rate became free, propulsion and retropulsion were abolished. The face became more expressive and the mood more normal. Patients who previously had to be fed were able to take nourishment without aid. Harmin, on the other hand, had no effect on the tremor. The combination of harmin and scopolamin is considered the most effective treatment of the postencephalitic state.

PEDIATRICS

UNDER THE CHARGE OF

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The Cholesterol and Bilirubin Contents of the Blood of Mother and Child.—HINGLAIS and GOVAERTS (*Gynec. et obstet.*, 1930, **22**, 137) found that, although hypercholesteremia in the mother is frequent at term, it is by no means a constant phenomenon. They observed a distinctly low cholesterol content of the blood in infants at birth. Although the hypothesis of placental origin of a part of the fetal cholesterol cannot be entirely eliminated, nevertheless the excess of cholesterol in the fetal suprarenals indicates an endogenous source of at least part of the cholesterol. They found no direct relationship between the maternal hypocholesteremia and the need of the fetus for cholesterol. The excess of cholesterol in the mother is valuable because of its antitoxic and antihemolytic qualities. During the first few days after birth the infant shows a rapid and marked increase of the cholesterol content of the blood. This seems, in part at least, to be due to activity of the suprarenals. It was seen that the cholesteremia increased more rapidly when absorption of the vernix caseosa was allowed than when the vernix caseosa was immediately removed by washing. There was found, however, no basis for the hypothesis of an amniotic origin of the cholesterol of the vernix caseosa. No direct relationship was found to exist between the excess of bilirubin in the blood at birth and the low cholesterol content of the blood. It was

observed that the bilirubinemia, which is the result of hemolytic processes, decreased during the first few days after birth. This is undoubtedly due to the fact that the increased cholesteremia exerts an antihemolytic influence that checks the production of bilirubin. It was also noted that the bilirubinemia decreased more rapidly in the infants whose vernix caseosa was absorbed, and in whom a more rapid increase of cholesterol was observed.

Strychnin Poisoning in Children.—Aikman (*J. Am. Med. Assn.*, 1930, **95**, 1665) emphasizes the danger of strychnin in laxative pills as well as the fact that the laxative combination clinically is as effective without this dangerous drug, which is often ingested by children because such pills have a candy coating. Strychnin poisoning is most common in children under five years of age, especially those between one and two years. The author feels that strychnin poisoning should be listed under a separate heading in listing causes of death. It is most often caused by accidentally eating medicine prepared for adults. Among the colored sugar-coated cathartic tablets that cause the most of the deaths are Hinckle's cascara and A. B. and S. tablets. Strychnin causes fatal convulsions in infants, and investigation has shown that it is not necessary for the efficacy of the tablets. The use and sale of strychnin should be controlled by legislation, but now is very poorly controlled. The elimination of the coating from tablets containing strychnin would prevent many cases of poisoning, as the unpleasant taste would insure against their ingestion by young children, in sufficient quantity to be poisonous. It is certain that strychnin is the most serious form of accidental poisoning in children under five years of age.

Extrinsic Congenital Stenosis of Duodenum as Anatomic Basis of Cyclic Vomiting.—Camera (*Arch. de méd. des enf.*, 1930, **33**, 583) reports a case of cyclic vomiting with acetonuria that he had studied for several years. From the first he was impressed by the resemblance of this condition to the symptoms produced by subvaterian stenosis of the duodenum. Roentgenologic study proved the suspicion of a duodenal stenosis, and the child was finally cured by an anastomosis between the first portion of the small intestine and the second portion of the duodenum, passing through the transverse mesocolon. The pathogenesis of so-called cyclic vomiting is as yet undetermined. The theories of acetonuria, appendicitis and hepatic disturbances have all been proved unreliable. The author is convinced that the character and syndrome of the gastroduodenal vomiting that is the chief feature of the disease may be explained, if one considers a subvaterian duodenal stenosis as its anatomic basis. The stenoses, whether total or partial, are caused by a lack or delay in the attachment of the mesocolon in which the entire large intestine has a tendency to fall into the small pelvis, and the mesenteric pedicle, because of this abnormal weight, compresses the duodenum against the posterior wall of the abdomen. Passage through the duodenum is thus blocked, and habitual constipation, migraine and sometimes hepatic intoxication result. The condition is also marked by periodic attacks of vomiting that correspond to those usually described as cyclic vomiting with aceto-

nuria. When the attachment of the mesocolon is merely retarded, as is common in early childhood, the attacks are of short duration. The high localization of the stenosis explains the persistence of the vomiting, the absolute intolerance of ingestion of any substance, and the rapid dehydration that results. Because of this localization of the stenosis, when the small free portion of the gastro-intestinal tube is relieved of its alimentary content, the vomitus can consist only of the secretions of the gastric and duodenal glands. This liquid mass, driven back toward the stomach, when it reaches its point of stenosis is emitted as by regurgitation when the pylorus is open or with painful contractions when the pylorus is closed. These are the two types of vomiting observed in cases of cyclic vomiting with acetonuria. The acetonuria itself as well as other concomitant toxic conditions that are often seen is the result of the mixing of the glandular secretions.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Problem of Early Genital Lesions.—WENGER, SURGEON and PROSKE (*Am. J. Syph.*, 1930, **14**, 313) discuss the problem of the differential diagnosis between chancre and chancroid based on 1235 genital lesions studied at the United States Public Health Clinic at Hot Springs. They believe that any diagnosis of a genital lesion unsupported by laboratory findings is questionable and that too much emphasis has been placed on clinical differentiation. A diagnosis of syphilis is established in the presence of the following data: (1) Positive darkfield for spirocheta pallida and positive Wassermann test; (2) positive darkfield and negative Wassermann; (3) negative darkfield and a positive Wassermann. A case of this sort is not necessarily early syphilis, however, and the genital lesion may prove to be chancroidal. The diagnosis of chancroid can be established by: (1) Demonstrating the Ducrey bacillus *by cultural methods;* (2) the test of time, that is, the inability to prove the presence of syphilis by repeated darkfields, gland punctures, and a series of Wassermann tests over a period of several months. The authors state that it is difficult to obtain the organism of chancroid in pure culture because of the usual presence of secondary infection both in the genital lesion and glands at the time the patient is first seen. Furthermore, the Ducrey bacillus is seldom found in suspected lesions by smear preparation because of its tendency to give up its characteristic streptobacillus form as soon as suppuration and

necrosis occur. Hence in most cases of chancroid the diagnosis must be made in retrospect after syphilis has been adequately excluded. In the present study a diagnosis of syphilis was established either by a positive Wassermann test or a positive darkfield examination, or both in 86 per cent of the entire series. The remaining 14 per cent constituted a difficult problem for most of the patients were indigent and failed to coöperate in the necessary Wassermann follow-up. Twelve of the patients, however, later returned to the Clinic with evidence of syphilis. Some undoubtedly acquired a subsequent infection but it is not likely that all the members of the group did.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Tuberculous Salpingitis.—Basing his statements on his experiences at Saranac Lake, JAMESON (*Am. Review of Tuberculosis*, 1930, **22**, 72) is of the opinion that involvement of the genital organs ranks fifth among the complications to which the woman suffering from pulmonary tuberculosis is liable. There is no syndrome of symptoms by which tuberculous pelvic disease can be distinguished from any other inflammatory variety but signs or symptoms of pelvic inflammatory disease in any woman showing evidence of tuberculosis elsewhere should be regarded with suspicion. It is customary to regard salpingitis in the virgin as tuberculous unless there has been a previous gonorrheal vulvovaginitis. Tuberculosis attacks the pelvic organs in about 8 per cent of women with pulmonary tuberculosis. In regard to the treatment of pelvic tuberculosis, he believes that the Roentgen ray seems to offer a feasible conservative method of treating lesions of the uterus and adnexa in women with tuberculosis of the lungs. In cases too sick for even this method of treatment, conservative treatment with hot douches, baking and general medical measures should give relief in a majority of cases, while surgery should be restricted to those cases not relieved by other methods. While the Reviewer feels that the above advice is good for the cases having lung involvement, a different situation is presented in the patients who have tuberculous salpingitis without obvious pulmonary disease. In such cases surgery frequently accomplishes brilliant results and the patients should not be denied operative treatment if a fair trial of nonoperative measures has failed to improve the pelvic condition.

Postmenopausal Bleeding.—Uterine bleeding which occurs after the menopause should always be a cause of concern to the attending physician until he has proven that it is not due to uterine cancer. It is well to remember, however, that all cases of this type of bleeding are not of a malignant nature. In a series of 179 cases of postmenopausal bleeding which were studied in the gynecologic department of the Johns Hopkins Hospital by TE LINDE (*South. Med. J.*, 1930, **23**, 571) a malignant condition was found somewhere in the generative organs in 60% and relatively benign conditions in 40%. The most common site of the malignant growth was the uterus (55.9%). Certain benign and malignant causes of genital bleeding after the menopause can be diagnosed by inspection of the vagina and cervix or curettage of the uterus, but in a small group of cases these procedures do not satisfactorily explain the symptom. In such cases the question of neoplasm of the ovary should be borne in mind, and even though no evidence can be discovered by palpation at the time of the curettage, the patient should be subjected to reëxamination quite frequently, and as soon as any increase in the size of an ovary can be made out she should be subjected to a laparotomy, provided her age or other physical condition does not present any serious contraindication. If curettage reveals hyperplasia of the endometrium several years after the menopause the presence of follicular oöphoroma or a granulosal cell tumor of the ovary is probably, and the patient should be kept under observation and subjected to laparotomy as soon as palpation shows any ovarian enlargement.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Treatment of Ocular Tuberculosis by Means of Roentgen Rays.—URBANEK, J. (*Brit. J. Actinotherapy*, 1930, **5**, No. 8, 169). Up to the present time we have no uniform dosage as regards the kind or quantity of Roentgen ray to be used in treatment of diseases of the eye. Following the advice of Rohrschneider regarding the standardization of dosage Urbanek applied Roentgen rays to tubercular diseased eyes. Reporting on the result of 50 cases treated in the first University Eye Clinic, Vienna, he found improvement in only 3 of 20 cases of chronic iridocyclitis. These cases had both eyes affected and only one eye was radiated. In this way he was able to observe in all 3 cases that a more rapid favorable termination of the process took place upon the eye which had been radiated. The results in scleritis were thought to be very good, but in one case when both eyes were involved the radiated eye showed no more rapid improvement than the other, though with "tebeprotin" a rapid cure was obtained in both eyes. In *old* cases of

choroiditis no beneficial results were obtained. On the other hand Roentgen ray treatments of fresh cases gave most excellent results. The result of treatments in cases of keratitis also were very good. In recurring hemorrhages in the vitreous humor no success was obtained. The treatments given in Professor Holzknicht's Institute were with $1\frac{1}{2}$ H. to 2 H. through a filter of 0.3 zinc, unless there was need for especial care on dosage. The dose corresponds to approximately 18% of H.E.D. The highest dosage given was 25 H., divided into 14 radiations, spread over a period of nine months. The first radiations were given at intervals of eight days; then came intervals of four to six weeks.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Incidence of Bacteria in 400 Tonsil Cultures.—It was Louis who gave us that important instrument of research—the Numerical Method—involving the careful collation and intelligent analysis of accurately observed facts. No one can deny that this system has provided clues leading to the solution of many formerly mysterious bacteriologic problems. And there is no reason to believe that the same plan will not aid materially in clarifying the fog enshrouding many etiologic phases of infectious disease at the present time. Furthermore, because this method is constantly available to each and every physician in his daily routine, the depth of its potential value remains unsounded. Consequently, in view of the difficulties in arriving at an established composite picture of the pharyngeal and oral bacterial cosmos, we continue to pursue our policy of abstracting selected revelant contributions. COBE (*J. Infect. Dis.*, 1930, **46**, 298) reports the bacteriologic findings of material obtained from the tonsils surgically removed from 400 persons. Most of the microörganism corresponded to well-known habitues of the oropharynx. Reckoned according to average mean total percentages, the incidence of the commoner bacteria were; staphylococci, 93; pneumococci, 58; streptococci, 42; M. catarrhalis, 27; B. influenzæ, 23; B. mucosus capsulatus, 21; diphtheroids, 11. Hemolytic streptococci occurred virtually as often as the viridans and nonhemolytic varieties combined. Three per cent of the nonhemolytic streptococci, which represented 14.5 per cent of the average mean total, were identified as *Streptococcus cardioarthritidis* (Small). More children harbored streptococci than adults. B. influenzæ, B. mucosus capsulatus and the diphtheroid bacilli prevailed in the spring; whereas M. catarrhalis was more prevalent in the fall.

RADIOLOGY

UNDER THE CHARGE OF

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The Interpretation of Sinus Roentgenograms.—Recalling that the Roentgen ray has been in use as a diagnostic aid in disease of the nasal accessory sinuses for at least fifteen years, GRIER (*Am. J. Roent. and Rad. Ther.*, 1930, **24**, 21) observes that during this period there has been less improvement in the method than in any other field of roentgenology. To improve the work close attention must be given to technical details, time must be taken for study of films, and the examiner should understand the pathology of sinus disease as demonstrated by roentgenologic changes. The last is a real stumbling block to progress, and the difficulties are increased by the fact that the roentgenologist and the rhinologist do not understand each other even when they attempt to coöperate. The common lesions which produce circumscribed areas of density are benign tumors, such as osteomas or fibromas; polyps, mucoceles, cysts, and hyperplasia of the mucosal lining. In most cases these changes can be recognized by the roentgenologist, but sometimes they cannot be classified definitely and the differentiation must be made on the history and clinical manifestations. Slight uniform opacity of the sinuses is seen in congestion of the mucous membrane, as in acute colds or hay fever; slight thickening of the membrane left after recovery from a previous attack of sinusitis; following operations in which the mucosa was traumatized; suppurative sinusitis with free drainage, and chronic hyperplastic sinusitis. Marked general opacity occurs in purulent sinusitis and extensive polyposis.

Roentgen Ray Findings in Erythroblastic Anemia.—Erythroblastic anemia, as described by MANDEVILLE (*Radiology*, 1930, **15**, 72) is a hemolytic anemia occurring in infancy and early childhood, characterized by enlargement of the spleen, dark-colored urine containing urobilin, moderate leukocytosis, and an extremely large number of erythroblasts in the circulating blood. Its etiology is obscure and only one patient with the disease is known to have reached adult life. Roentgenologic manifestations in the bones have been noted as follows: (1) Thickening of the medullary portion of the frontal, parietal, temporal and occipital bones; (2) thinning of the inner and outer tables of the bones of the skull vault; (3) a mottled appearance of the medullary portion of the cranium in the earlier stages, described by several authors as a spongy or porous appearance; (4) striations perpendicular to the tables of the skull in the later stages, with the diploe gradually assuming a thickness equal, at times, to as much as four times its normal width;

(5) irregular trabeculations in the pelvis, vertebræ, ribs, clavicle and scapulæ, the appearance of which is apparently due to new bone formation; there is evidence of slight rarefaction within the trabeculated areas, which has been described as a porous appearance, which is evidently due to localized destructive bone changes; (6) definite thinning of the cortex of the long bones, an important and rather constant finding; (7) rarefaction of the shafts of the long bones, the medulla of the long bones demonstrating increased radiability, which characteristic is well illustrated and described by some authors as a transparent medulla; (8) trabeculations of the medulla of the long bones, more marked in the metaphyses, which appear as sharp and finely penciled trabeculæ near the ends of the bones; some authors have described them as trabeculations perpendicular to the cortex, but this Mandeville has found not to be the rule; the trabeculation may affect all of the bones of the body; (9) normal joints, no pathologic change having been noted to involve the joint surfaces or spaces; (10) no periosteal elevation, periosteal involvement not being recorded, and (11) absence of pathologic fractures. Distinction of these manifestations from those produced by certain other anemias, chloroma, syphilis and metastasis is difficult.

NEUROLOGY AND PSYCHIATRY

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Pineal Cysts: With Report of Two Cases.—HANDLEY and MANCH (*J. Ment. Sci.*, 1930, **76**, 250) reports the clinical and postmortem findings on 2 cases of pineal cysts, both medium-sized. Careful analysis of these cases leads him to conclude that the primary diagnostic features of pineal cysts are: (1) the age of the patient—about forty years (tumors occur between ten and twenty-five years; (2) rapid progression—death within a month (tumors take a year or more); (3) sequence of anxiety, vivid hallucinations, confusion and sleep disturbance; (4) neurologically: increased intracranial pressure syndrome, rapid in onset and of high degree, to some extent simulating a cerebellar lesion; paralysis of eye muscles, together with pupil changes, increasing deafness and tendency to weakness of lower limbs. Surgical treatment is suggested. There may occur spontaneous relief, by the cyst squeezing through and appearing from underneath the splenium.

Postencephalitic Parkinsonism With Psychosis.—ALPERS (*J. Nerv. and Ment. Dis.*, 1930, **72**, 257) records 3 cases of postencephalitic Parkinsonism all of which are accompanied by psychoses. One case came

to necropsy. Comparing this case with that reported by Hassin and Rotman, he believes that the psychoses developed during the course of a postencephalitic Parkinsonism are not incidental, but are due to encephalitis which in these instances causes a more wide-spread pathologic process than is seen in the usual case of postencephalitic paralysis agitans. All of the 3 cases reported here had hallucinations, chiefly auditory but sometimes visual, without clouding the sensorium or marked changes in mood or affect. The second case showed periods of confusion. The cases are considered of interest, because of the infrequency of hallucinatory trends in psychoses accompanying Parkinsonism.

The Boltz (Acetic-anhydrid) Test in Cerebrospinal Fluid.—Thomas (*J. Ment. Sci.*, 1930, **76**, 271) presents the results of analysis of acetic anhydrid reactions in 48 tests performed. In 23 of the cases positive reactions were obtained and in 25, the reactions were negative. Of the 23 positive cases, all were cases of general paresis and showed other syphilitic reactions. Of the 25 cases which were negative, 11 showed positive syphilitic reactions and 14 were completely negative in that respect. That is, of 34 cases showing evidence of syphilis by other serologic examination, 23 were positive and 11 were negative. The results throw doubt on the value of the Boltz test. There is some discussion of the effect of treatment on the test.

PATHOLOGY AND BACTERIOLOGY

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Multiple Gummas of the Heart in the Newborn.—Williams (*Am. J. Path.*, 1930, 6, 573) has reported in this paper, a case of gumma of the heart in a negro infant that died a few hours after birth. No syphilitic lesions, other than those of heart, were found. The largest measured 1.25 by 0.5 by 0.5 cm. and was situated in the anterior wall of the left ventricle near the interventricular septum. Two other smaller lesions were present near the interventricular septum, one anteriorly and the other posteriorly situated. The nodules were firm, swollen and well demarcated, protruding slightly. Small areas of softening were present in their centers. Sections of the nodules stained by Levaditi's method showed numerous spirochetes, about the bloodvessels and in intercellular spaces. In sections stained with hematoxylin and eosin, the muscle fibers appeared shrunken and prominently striated while in some areas they were separated by varying amounts of a mucoid vacuolated débris. This material was infiltrated with lymphocytes,

plasma cells, monocytes and polymorphonuclear leukocytes, which were also to be noted in the perivascular areas and beneath the epicardium. The author questioned the advisability of applying the term gumma to such lesions which do not conform microscopically to the typical picture of gumma. He suggested the term "localized syphilitic cellulitis" and "fulminative syphilitic myositis" as being more descriptive of the condition.

The Significance of the Muscular "Stroma" of Argentaffin Tumors (Carcinoids).—In a study of a number of argentaffin tumors of the appendix, MASSON (*Am. J. Path.*, 1930, **6**, 499) found that the proliferating argentaffin cells penetrated electively the nerves of the myenteric network. Invasion of connective tissue and of lymphatics was secondary and muscle fibers did not originate in these situations. Invasion of the nerves, on the other hand, produced a localized hypertrophy of the muscle bundles supplied by the nerves involved. The author concluded therefore that the muscle fibers found in the interstices of carcinoid tumors were not an integral part of the tumors, but resulted from the proliferation of preëxisting muscle fibers, stimulated by the presence of the tumor in the nerve fibers supplying them. The stimulation was thought to have been produced through the agency of a hypothetical substance (neurocrinia) of low diffusibility which was elaborated by the tumor cells and which acted upon the nerves. Attention was drawn to the possibility that a similar substance produced by the normal argentaffin cells of the intestinal mucosa may act in a similar way and thus play a rôle in the functioning of the muscularis mucosa.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Anterior Poliomyelitis in Massachusetts, 1907-1929.—FORSBECK and LUTHER (*Boston Med. and Surg. J.*, 1930, **203**, 1115) state that in Massachusetts there has been little change in the case rate and mortality rate during the past twenty-three years. The relationship between mortality rate and case rate has not been marked. There is apparently a periodicity in the incidence of poliomyelitis and evidently the fatality rate is higher for years of high mortality. The seasonal distribution for poliomyelitis is similar to that for the United States Registration Area; the peak occurs in September. There is apparently no relationship between time of the peak and the size of the year's incidence. There is now a tendency for the peak to occur later in the year than formerly. The large number of cases studied shows a ratio of about

77 females to every 100 males. This discrepancy is even greater during adolescence. There is a significant relationship between age of incidence and density of population, the cases occurring somewhat later in life in rural communities. However, there is apparently no significant difference in the case rate in rural and urban communities. Since 1918 there has been a striking change in the age distribution of poliomyelitis as a whole. The number of cases in the age group ought to four has markedly decreased, while there has been a compensatory increase in the relative number of cases in the age group five to fourteen. The percentage of cases in adult life has remained quite constant.

The Influence of Ultraviolet Radiation on the Weight of Adult Rabbits, Normal and Syphilitic.—HARNES (*J. Exper. Med.*, 1930, **52**, 253) found that normal rabbits living in total darkness and exposed to ultraviolet radiation at regular intervals showed a more rapid rate of increase in weight than animals living under the same condition, but after an initial period of rapid increase the irradiated animals maintained a lower body weight than those living in the dark. Under the same conditions animals inoculated with T. pallidum and exposed to ultraviolet light maintained a lower weight than the corresponding control groups living in total darkness. Furthermore, the mortality rate from pneumonic infection was found to be greater in animals exposed to ultraviolet radiation than in those living entirely in the dark. It is evident, therefore, that, under the conditions given, ultraviolet radiation was detrimental rather than beneficial.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 15, 1930

Certain Immunologic Studies in Insulin Sensitivity.—W. G. KARR, W. A. KREIDLER, C. W. SCULL, O. H. PETTY (from the Laboratory of Physiologic Chemistry, Graduate School of Medicine, University of Pennsylvania). A diabetic patient showed a marked sensitivity to insulin which persisted throughout twenty months of insulin therapy. There was a marked local reaction at all times about the site of injection. There was a diffuse swelling, the area became red and hot and pain developed which persisted for twenty-four hours or more. There was a gradual increase in the insulin required to keep the diabetes under control until about fourteen months after the therapy was instituted, when the patient was receiving 600 to 700 units daily. Certain studies were made on the patient at the time.

Intradermal skin tests gave typical wheal reactions to insulin made from pig pancreas as well as beef, also to a solution of crystalline insulin furnished by the courtesy of Dr. E. M. K. Geiling, of Johns Hopkins University, Baltimore. The Praussnitz-Kustner passive transfer test was also positive. Some of the patient's serum set up with insulin

gave a precipitin reaction which was negative with normal and other diabetic serum. Mixing the patient's serum with insulin *in vitro*, and injecting appropriate amounts into rabbits gave no evidence of a combination or any inhibition when the test was compared with a similar one containing normal serum.

Using the patient's serum as the activating antigen, rabbits were sensitized by gradually increasing dosages over a period of two to three weeks. This rabbit serum showed allergic antibodies by the precipitin test, using insulin alone as the antigen. Control experiments, using normal serum, other diabetic serum and insulin and saline, were uniformly negative. These allergic antibodies were only produced in the rabbit when the patient's serum was used as the activating antigen. Some of this active rabbit serum was given to the patient. As the patient was sensitive to the rabbit serum, she was desensitized and then 5 cc. given intramuscularly. After a period of about one week she developed insulin shock symptoms, and her insulin requirement fell very rapidly from 650 units to about 150 units. It remained at about this level for about one month, when it was possible to discontinue insulin entirely. The fasting blood sugars were normal, and the carbohydrate in her diet was increased. A glucose-tolerance test, however, showed a diabetic curve, and the patient was again put on a moderately low carbohydrate diet, although the fasting blood sugars were normal.

The Effect of Narcotics (Urethanes) on Permeability of the Living Cells to Water.—Balduin Lucké (from the Department of Pathology, University of Pennsylvania). Former studies have shown that in the presence of cations of two or more valences the permeability of the cell to water is of very low order of magnitude.* For example, cells, such as the unfertilized egg of the sea urchin, whose natural medium is sea water, have a value of permeability of about 0.05, that is, 0.05 cubic microns of water pass through each square micron of cell surface per minute, under the driving force of 1 atmosphere of osmotic pressure. This surprisingly low degree of permeability to water is presumably due to the high concentration of calcium and magnesium in sea water. All attempts further to decrease permeability have so far been unsuccessful. However, it has been reported that narcotics lower permeability to water. The question, therefore, arose whether narcotics in the presence of sea water, or narcotics in any solution containing bivalent or higher valent cations would reduce permeability to water beyond the value obtained in sea-water alone.

Permeability to water in unfertilized eggs of the sea urchin was studied by measuring the rate of swelling in hypotonic sea water containing various urethanes in narcotic concentration. It was found that these narcotics in the presence of sea water do not decrease the permeability.

Since the presence of bivalent cations may mask the action of narcotics, the experiments were repeated in hypotonic dextrose solution. It was now found that narcotics have a tendency to reduce permeability to water, being, however, much less effective in this respect than are cations of two or more valences. The conclusion may be

* Journal of General Physiology, 1928, **12**, 129; 1929; **12**, 571.

drawn that the effect of narcotics on cell permeability to water depends on the composition of the medium in which the narcotizing compounds are dissolved.

The Relief of Milk Anemia by Amino Acids.—D. L. DRABKIN and H. K. MILLER (from the Department of Physiologic Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). A study has been made of the relief of milk anemia by feeding milk supplemented by 0.2 mg. of iron per rat per day and various amino acids. The effect upon hemoglobin concentration in these experiments may be ascribed directly to the amino acids fed. Control experiments have indicated that the above quantity of iron is in itself insufficient to check the progress of the anemia. Analyses have established that the various amino acids fed were negative for copper and contained only negligible traces of iron.

The feeding of arginin, glutamic acid and their salts resulted in a continuous increase in hemoglobin concentration, indicative of a recovery from the anemia. With sodium aspartate, pyrrolidone carboxylic acid, tryptophane and prolin an initial increase in hemoglobin concentration was observed. With these amino acids, however, the recovery from the anemia was not progressive. The hemoglobin concentration was either maintained at the higher level or once again fell. The administration of alanin, alanin hydrochlorid, histidin dihydrochlorid and hydrochloric acid failed entirely to check the anemia.

In an ineffective trial,* in one case of pernicious anemia, glutamic acid was found to be of no value, as judged by the usual criteria of effective therapy in this form of anemia.

The Effect of "Folliculin" on the Motility of the Uterus in Vivo.—S. R. M. REYNOLDS (from the Department of Physiology, University of Pennsylvania). Several workers (Frank, Bonham and Gustavson;[1] Brouha and Simonnet[2]) have reported that œstrus-producing extracts produce contractions in the uterus of the castrate animal which resemble contractions of uteri obtained from animals in heat; this is so when the fluid is injected into the animal twenty-four to forty-eight hours before excision of the uterus. The latter investigators report[3] that an *immediate* response is obtained when œstrin is added directly to the bath in which the uterus is immersed. Furthermore, they say that washing a contracting uterus from an animal in heat for twenty minutes will abolish all spontaneous activity. This has not been confirmed. Moreover, other workers are not in agreement with these results: Fraenkel[4] reports negative results, and Bourne and Burn[5] find that only "especially sensitive" uteri respond to œstrin. We believed that records from uteri of unanesthetized animals might yield some valuable data on this point.

We have used "theelin," prepared and described by Veler, Thayer and Doisy,[6] and supplied to us by Parke, Davis & Co., in ampules, stated to contain 50 rat units per cubic centimeter. The route of administration has been intravenous to obviate variable factors in absorption. Four injections are made over a period of eight hours. In no case has the sum total of the four injections exceeded 1 cc. Only

* By Dr. Thomas Fitz-Hugh of the Department of Medicine.

rabbits immediately postpartum, and so in heat, are used; they are castrated three to four days later. One series of animals is injected four days, a second series twenty-one days, after castration.

In a series of recently castrated animals we have found that 5 rat units (0.1 cc.) theelin-kilo body weight over eight hours will produce the following effect: The quiescent or small, irregular activity of the uterus of the castrated animal is changed to a small rhythmic type of activity in eight hours; by sixteen hours the activity is in some cases increased, in others not until twenty-four to thirty hours is there a marked increase. Large rhythmic contractions may persist until the second day, in others the peak of activity is over and the activity subsides in the course of four to six days. We regard as significant 2 cases in which only 2 rat units (0.04 cc.) theelin-kilo in eight hours produced a marked effect. It was not as abrupt in its onset as prolonged in duration, however, as with larger quantities of theelin. These two cases betoken a sensitivity six times greater than that found in rat standardization technique. It appears that in twenty-one day castrated animals, six to ten times the quantity of theelin must be used to produce effects comparable to those obtained in recent castrates with lesser quantities of theelin.

The significance of these results cannot be estimated at present, although it would seem that they are not inconsistent with the current, yet inadequately proven notion that the large contractions seen in a uterus at œstrus may be attributed to a hormone colloquially spoken of as "folliculin." Our understanding of its rôle in parturition or uterine dysfunction must await further investigation.

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